ESSAYS ON OUTPATIENT ANTIBIOTIC CONSUMPTION

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To my parents, and in loving memory of my brother† and grandmother†

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Contents

Introduction

The inappropriate use of antibiotics represents a growing concern in many countries. There is strong evidence that antibiotic consumption leads to the development of bacterial resistance, which undermines antibiotic effectiveness and increases the cost for society. Moreover, the increasing mobility of individuals and the consequent increase in the risk of spreading infections across geographic areas exacerbate the problem and represent a serious threat to public health worldwide. The investigation of factors explaining antibiotic consumption across and within countries could help to disentangle inefficiencies in consumption and design strategies to optimise antimicrobial use in the community. The aim of this thesis is to investigate economic aspects of antibiotic consumption in the community. The research is divided in three essays.

In the first essay we focus on determinants of antibiotic use in Italy and the spillover effects of antibiotic consumption across regions. The literature on socioeconomic determinants of antibiotic consumption in the community is limited to few countries using cross-sectional data. We analyse regional variations in outpatient antibiotics in Italy using a balanced panel dataset covering the period 2000-2008. We specify an econometric model where antibiotic consumption depends upon demographic and socioeconomic characteristics of the population, the supply of health care services in the community, individuals' health status, and antibiotic copayments. The model is estimated by means of ordinary least squares techniques with fixed (FE) and random effects (RE). The implications of consumption spillovers across geographical areas are investigated by means of spatial-lag and spatial-error models (SLFE and SEFE). We find significant and positive income elasticity and negative effects of copayments. Antibiotic use is also affected by the age structure of the population and the supply of community health care. Finally, we find evidence of spatial dependency in the use of antibiotics across regions. The results suggest that the understanding of factors contributing to socioeconomic inequalities in the utilization of antibiotics in outpatients may help to design effective policy interventions to fight the threat of bacterial resistance. Moreover, regional policies (e.g. public campaigns) aimed at increasing efficiency in antibiotic consumption and controlling bacterial resistance may be influenced by policy makers in neighbouring regions. There will be scope for a strategic and coordinated view of regional policies towards the use of antibiotics.

In the second essay we focus on the dynamic of antibiotic consumption and the behaviour of consumers. To some extent, antibiotics are similar to addictive goods, since current consumption is reinforced by past use because of bacterial resistance, which represents a growing concern in many countries. Consequently, the purpose of the second essay is to explore how consumers adjust their current level of antibiotic consumption towards desired levels over time. We use a panel dataset (2000-2008) for 20 Italian regions and estimate a dynamic model where antibiotic consumption depends upon demographic and socioeconomic characteristics of the population, the supply of health care in the community, antibiotic price, and the "capital stock" of endogenous bacterial resistance measured by past consumption. We apply alternative dynamic estimators for short panels: the bias-corrected least squares dummy variable (LSDVC) and the System Blundell-Bond GMM estimator (GMM-BB). The estimation results are stable across different model specifications and show that antibiotic use in previous periods has a positive impact on current antimicrobial consumption (between 0.38 and 0.48). This indicates that the process of adjustment to desired levels of consumption is relatively fast (approximately 1.6 - 1.9 years). Weak persistence in consumption may suggest that individuals are responsive to changes in antibiotic effectiveness.

Finally, the third essay investigates the impact of national policies towards a rational consumption of antibiotics. Because of evidence of causal association between antibiotic

use and bacterial resistance, the implementation of these policies has emerged as a valid tool for controlling and reversing bacterial resistance. However, the impact of public policies, precisely public education campaigns, has not been assessed accurately at the moment. To disentangle this impact we control for the effects of main socioeconomic determinants of consumption as well as epidemiological factors. Comparable data on systemic administered antibiotics and socioeconomic determinants in 21 European countries are available for a 11-years panel between 1997 and 2007. Data on national campaigns are drawn from the public health literature. Using a difference-in-differences approach, we estimate an ad-hoc econometric model with fixed effects. Lagged values and instrumental variables approach are applied to address endogeneity aspects of the prevalence of infections and the adoption of national campaigns. We found that public campaigns significantly reduce the use of antimicrobials in the community in all the estimations. Their effect is robust across different measurement methods. Main determinants of antibiotic consumption (demographic structure and density of general practices) remain highly significant. Further research is needed to investigate whether policy interventions to contrast the threat of bacterial resistance is more effective if targeted to specific social groups (general practitioners or patients).

Antibiotic consumption in Italy: a spatial panel approach

1. Introduction

The increasing use of antibiotics and the consequent harmful effects of bacterial resistance represent a growing problem in many countries. Evidence suggests that bacterial resistance grows with antibiotic use (Monroe and Polk, 2000; Mera *et al.*, 2006). Although the effects of intervention policies on resistance to antimicrobial drugs cannot be assessed accurately at present, public interventions may be effective in controlling antibiotic consumption (Huttner *et al.*, 2010). Consequently, the investigation of socioeconomic inequalities in the use of antibiotics across geographic areas is an important approach in understanding causes of consumption and building effective intervention policies.

Literature shows that outpatient antibiotic consumption, measured by the number of defined daily doses per 1,000 inhabitants (DID), is highly heterogeneous across European countries (Elseviers *et al.*, 2007). For instance, the consumption of antimicrobials in France is almost three times the consumption in the Netherlands. Generally, southern European countries exhibit higher levels of consumption as compared to northern European countries.

Outpatient antibiotic consumption is also highly heterogeneous across geographic areas within a country (Kern *et al.*, 2006). To our knowledge, the study of socioeconomic determinants of consumption has been applied to few countries (Matuz *et al.*, 2005; Filippini *et al.*, 2006; Nitzan *et al.*, 2010). Since previous studies are based on cross-sectional data, unobserved heterogeneity may stem from omitted common variables that affect geographic areas differently. These latent common factors may induce cross-section dependence and lead to inconsistent estimation coefficients in regressions if hidden aspects are correlated with the explanatory variables (see Cameron and Trivedi, 2005).

Spatial econometric approaches to antibiotic consumption are lacking. Geographic areas are usually treated as isolated entities, ignoring the fact that antibiotic consumption is plausibly affected by consumption in neighbouring regions. Spatial interactions in panel data are considered, for instance, by Revelli (2001) to investigate variations in tax rates across English districts. As for antibiotics, spatial aspects are partially addressed in recent studies by Filippini *et al.* (2009a, 2009b) using cross-sectional data. Spatial dependency plays an important role in the use of antibiotics for two main reasons. First, antibiotics are used to cure infections which may spread to other individuals in the community. Second, antimicrobial resistance partially generated by the intensive use of antibiotics may reduce antibiotic effectiveness for other individuals in the community. It follows that regional policies (e.g. public campaigns) aimed at increasing efficiency in antibiotic consumption and controlling bacterial resistance could blunt the impact of policies in neighbouring regions through the generation of local spillovers. This may suggest that the lack of coordination of regional policies towards the use of antibiotics leads to inefficiency.

The purpose of this study is to investigate socioeconomic factors affecting regional variations in outpatient antibiotic use in Italy over a relatively large period of time (2000-2008) by means of panel data analysis which takes the external effects of consumption into account. The use of panel data makes it possible to specify fixed regional effects in order to take the unobserved heterogeneity into account. A novelty of our work is that it focuses on a country, Italy, of which socioeconomic determinants of antibiotic use in outpatients have not been investigated so far. The relevance of this focus also originates from the peculiar organization of the Italian health care system, which is based upon a National Health Service where the provision of health care is substantially devolved to regional health authorities. A question arises as to whether the effects of main socioeconomic determinants of consumption are similar in countries with different health care organizations, since previous studies are conducted in health care systems based upon health insurance plans.

According to a recent report of the European Commission (2010), Italy is the most consuming country of antibiotics in Europe with relatively poor levels of public awareness of antibiotic efficacy. This suggests that the investigation of factors affecting the use of antibiotics may raise more concern compared to other countries. Similarly to previous studies, our model hypothesises that regional consumption of outpatient antibiotics in Italy depends on antibiotic price (copayments), population age structure and income, the supply of health care services in the community, and the health status of the population. The model is estimated by means of ordinary least squares with fixed effects (FE). Consumption spillovers between regions are investigated by means of spatial-lag and spatial-error models with fixed effects (SLFE and SEFE). Spatial lags may reflect interactions between regions whereas spatial errors occur because regions have unobserved factors in common.

The remaining of the paper is organized as follows. Section 2 provides an overview of the literature on socioeconomic determinants of antimicrobial use across geographic areas. In section 3 we summarise the main features of the Italian market for primary care and antibiotic use in outpatients. The specification of the econometric model and estimation approaches are presented in Section 4 and Section 5, respectively. Section 6 discusses the results and section 7 concludes.

2. A review on socioeconomic determinants of antibiotic consumption

The literature on socioeconomic determinants of outpatient antibiotic consumption is limited to few empirical studies, although there are more general studies on the determinants of pharmaceuticals use (e.g. Costa-Font *et al.*, 2007). We present five studies which investigate the impact of socioeconomic factors within countries.[1] The main features of these studies –geographical setting, type of data, methodological approach, determinants considered and results- are summarised in Table 1.

Reference	Country	Data	Methodological approach	Main determinants considered	Main results
Nitzan *et al.* (2010)	Israel	8 districts annual data 2003 - 2005	Analysis of variance test, Kruskall-Wallis test, Pearson correlation, univariate and multivariate analysis	Age structure, gender, ethnicity, individual's choice of outpatient clinic, prevalence of chronic diseases	There are large differences in antibiotic use between geographic regions. The highest consumption is noted in the youngest age groups. The study shows that a higher prevalence of *diabetes mellitus* is associated with antibiotic use.
Filippini *et al.* (2009)	Switzerland	240 small areas quaterly data 2002	Two-stage least squares regressions with spatial lags	Income, age structure, incidence of bacterial infections, density of physicians and pharmacies, antibiotic price, and cultural aspects	Individual income, the demographic structure of the population, physician density and the price of drugs are all relevant determinants of local variations in the use of antibiotics in the community.
Kern *et al.* (2006)	Germany	23 areas in 16 states annual data 2003	Descriptive statistics of consumption and graphs	Population density, percentage of elderly individuals and non-German citizenship, income, GDP, unemployment, number of physicians and pharmacies per population, hospital facilities	The eastern states are low consumption regions. Relatively low antibiotic consumption is also seen in southern states. Relatively high consumption areas are in the west, near Luxembourg and the French and Belgian border. The regional pattern of use is similar for children and adults .
Filippini *et al.* (2006)	Switzerland	26 cantons quaterly data 2002 - 2004	Ordinary least squares, generalized least squares, and two-stage least squares regressions	Income, antibiotic price, physicians' density, age structure, level of education, share of foreigners on total population, incidence of infections and cultural differences.	Outpatient antibiotic consumption is significantly related to per capita income, antibiotic price, the density of medical practice, demographic, cultural and educational factors, and the incidence of baterial infections.
Matuz *et al.* (2005)	Hungary	19 counties annual data 1996 - 2003	Two-tailed Spearman coefficient for non-parametric correlations	Population density, prevalence of chronic diseases, age structure, income, GDP, number of individuals receiving free pharmaceuticals and social assistance, density of pharmacies, number of enrolled patients per general practitioner and yearly number of consultations.	Constant and large interregional differences in antibiotic consumption are observed in Hungarian ambulatory care. These differences are associated with socioeconomic determinants such as the fraction of the population having access to free medicines or receiving regular social assistance.

Table 1: Studies on socioeconomic determinants of antibiotics in outpatients.

[1] Regarding cross-country studies, we refer the reader to the recent analysis by Masiero *et al.* (2010) using European data.

Nitzan *et al*. (2010) analyse the use of antibiotics in outpatients in 8 districts of Israel. The authors investigate consumption measured in defined daily doses per 1,000 inhabitants for different age groups and for different groups of antibiotics. The study shows a decline in antibiotic use in all districts between 2003 and 2005 and large variation between districts. Results reveal that during the 3 years of the study the highest antibiotic consumption rates are observed for the youngest age groups (0-4, 5-18, and 19-44). Antibiotic consumption among individuals aged 65 or above is by far the lowest in all the age groups, probably due to higher hospitalization rates. Also, there is a significant association between a higher prevalence of diseases, such as diabetes *mellitus*, and higher antibiotic consumption. Conversely, higher rates of hospitalization seem to be correlated with lower levels of antibiotic consumption. Finally, the authors find large variability between the districts in the use of specific antibiotic groups. The use of penicillins in high consumption districts, for instance, is 2.8 times the use in low consumption districts. The magnitude of differences raises to 3.9 in the use of first-generation cephalosporines.

To investigate the socioeconomic determinants of outpatient antibiotic use in Switzerland, Filippini *et al*. (2006) use regional consumption data and regress them against a set of variables suggested by the literature as plausible causal factors of the demand for drugs. The dataset includes quarterly data for 3 years (2002-2004) detailed at cantonal level (26 cantons). Findings show that Switzerland uses relatively low volumes of antibiotics in ambulatory care compared to other European countries, but large differences are observed across cantons. The authors specify an *ad-hoc* demand function for the cantonal *per capita* outpatient antibiotic use which depends upon the health status of individuals, income, antibiotic price, age, education, density of physicians and cultural aspects summarised by linguistic groups and borders with other countries. Since individuals health status and antibiotic price can be endogenous, the authors consider the inclusion of lagged values in the model and apply an instrumental variable approach. The *per capita* income, antibiotic price, the proportion of foreign residents, the density of medical practices, and cultural and educational differences are significant determinants of consumption. Among these results, it is worth noting that income has a positive impact on consumption, and antibiotic price has a negative and significant effect, as expected. Conversely, physician density is associated with higher levels of antibiotic use.

Kern *et al.* (2006) carry out an exploratory analysis on antibiotic prescriptions in Germany for the year 2003. They investigate variations across 23 areas in 16 states in outpatient antibiotic use both for overall use and for specific antibiotic drug classes. Relatively low antibiotic consumption was observed in eastern and southern regions. Basic penicillins are the most frequently prescribed drugs with large regional variation. Regional patterns of use are similar for children and adults, although lower levels of consumption for children were observed in the south. The study does not find an association between overall antimicrobial consumption and population density, the percentage of elderly people, income, unemployment, gross domestic product and aspects of local health care supply, but the analysis lacks of a sound econometric approach.

Filippini *et al.* (2009a) investigate inefficiencies in the use of outpatient antibiotics across small areas. The authors carry out econometric estimations using a two-stage least squares procedure on quarterly data of antibiotic use (in DID) in Swiss outpatients available for 240 small areas in 2002. A model is proposed in which antibiotic use varies according to the socioeconomic and demographic characteristics of the population, the incidence of infections, the local supply of health care and antibiotic price. The results suggest a positive relationship between antibiotic consumption and income, the proportion of children between 0 and 14 years of age, the percentage of foreigners in the total population, the incidence of infections, and density of pharmacies and physicians. On the other hand, antibiotic price and the proportion of individuals over 74 years of age show a negative and significant impact on antibiotic use. Some seasonal effects are found, which suggests that the *per capita* outpatient antibiotic use is lower in spring and summer periods. Finally, the authors consider the effects of spatial dependency in antibiotic consumption across the areas by means of spatial lags included in their model. The negative impact of antibiotic use in neighbouring areas suggests that the use of antibiotics in one area may reduce the spread of infections in neighbouring areas.

Finally, Matuz *et al.* (2005) investigate regional variations in antibiotic consumption in ambulatory care in Hungary. The sample is composed of 19 regions (counties) for the years 1996-2003. The authors find that antibiotic consumption is 21.1 DID in 1998, close to the European average, but decreases from 2002. The study shows large and stable interregional variations in consumption. The ranking of regions according to total antimicrobial consumption is basically the same during the whole period. The authors test associations between total antibiotic consumption and possible determinants of use by means of the two-tailed Spearman coefficient for non-parametric correlations. They do not find any significant relationship between antibiotic consumption and the average monthly net income nor with the demographic structure of the population. Conversely, a significant association with total antibiotic consumption is observed with the proportion of individuals receiving free access to selected medicines from the public health system without quantity limit and the proportion of individuals regularly receiving social assistance.

3. Outpatient antibiotic consumption within the Italian NHS

The Italian health care system is based upon a national health service (SSN) mainly financed by general taxation and characterised by universal access to health care for the entire population and asymmetric decentralization of health care provisions to the 20 regions. Reforms over the 90's gave administrative and financial responsibility in the provision of health care to the regions. The central government retains limited supervisory control and continues to hold overall responsibility for the SSN to assure access and equal levels of health services across the country. The regions organise services that are designed to meet needs of their specific populations, define ways to allocate financial resources to the local health authorities (LHAs) within their territories, monitor health care services and activities provided by LHAs, and assess their performance.

Outpatient care in Italy is provided by general practitioners (GPs), paediatricians and specialists. General practitioners and paediatricians deliver primary care and preventive medicine and are mainly paid on a capitation basis. Generally, patients do not pay for visits to GPs. They also enjoy considerable freedom of choice of providers since they are only obliged to use providers in the province in which they reside and they must have a doctor's prescription for most forms of care. Patients can always change their GP within the province of residence (Atella *et al*., 2003). Specialists delivering outpatient care are paid on a fee-for-service basis. Patients pay only a small fraction of the full cost of a consultation if they are referred by their GP.

Medicines in outpatient care are classified in two categories. The first category (class A) includes essential medicines and medicines for serious and chronic diseases which requires a doctor's prescriptions. These drugs are fully reimbursed by the SSN although patients bear small copayments in some regions. Antibiotics are generally included in this category and copayments (ticket) include both a cost-sharing scheme and a reference pricing one.[2] According to this, patients are required to contribute to the cost of antibiotics either by a fixed amount per prescription or by a proportional-to-final price amount, or by paying the difference between the final price and the reference price.[3] People with chronic or rare

[2] In Italy only 1% of antibiotic courses are obtained from a pharmacy without a prescription (European Commission, 2010).
[3] See Fiorio and Siciliani (2009) for details.

diseases, disabled people, pregnant women and low income generally enjoy exemptions. The reference price is set for drugs which contain the same active ingredients, identical pharmaceutical dosage and package size. The second category of drugs (class C) includes medicines for minor diseases and ailments, medicines which use is discouraged and those not requiring a medical prescription. Pharmaceutical products included in this category are not reimbursed by the SSN.

Italy is a relatively high-consuming country for outpatient antibiotics. Using available data from the European Surveillance of Antimicrobials Consumption (ESAC) between 2000 and 2007 we can rank Italy among European countries according to the number of defined daily doses per 1,000 inhabitants (Figure 1). Italy ranks among the most consuming countries, just below Greece, France, Slovakia and Luxemburg. In contrast, the Netherlands, Austria, Germany and Denmark are among the less consuming countries. However, a recent survey by the European Commission (European Commission, 2010) indicates that Italy exhibits the highest proportion of antibiotics utilization in Europe between December 2008 and November 2009. Moreover, the majority of the population (51%) think that antibiotics are effective against cold or flu. The relatively high consumption of Italy raises concern about efficient antibiotic use in the country.

The mean level of consumption of outpatient antibiotics in Italy between 2000 and 2008 was 23.52 DID, with a peak in 2008 (25.01 DID) and a minimum in 2000 (22.36 DID)[4]. Figure 2 shows that antimicrobials use has been roughly stable over the period but a remarkable degree of heterogeneity in consumption is observed across the regions. Generally, regions in central Italy use more antibiotics *per capita* (24.94 DID) than regions in the north (18.42 DID) and less than southern regions and the islands (27.91 DID).

[4] Data are collected by the Italian agency for drugs (AIFA).

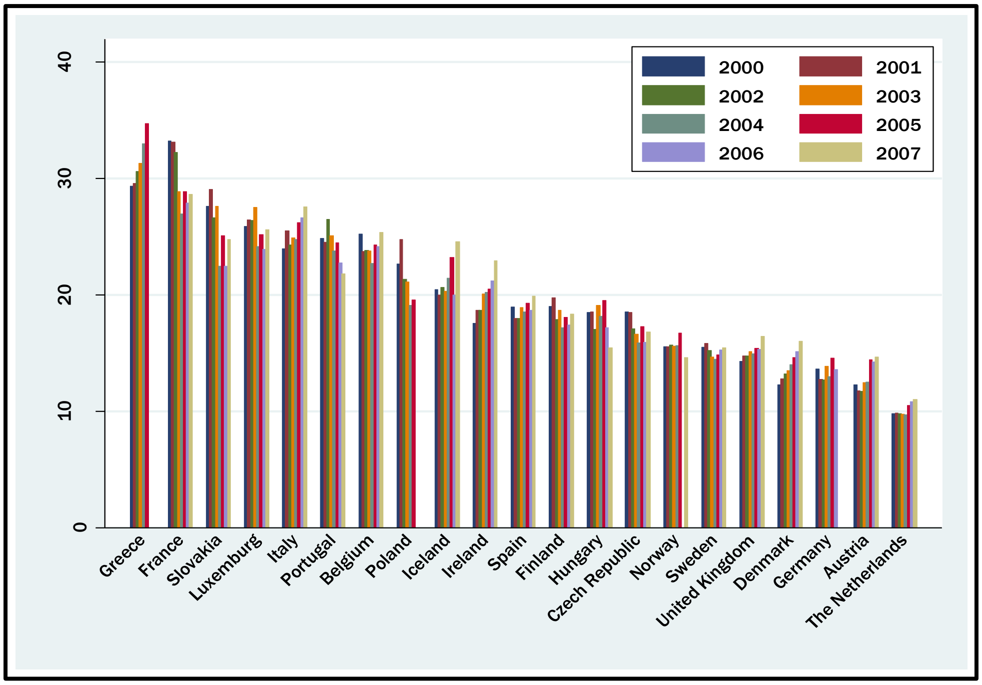

Figure 1: Antibiotic use in Europe by country (2000-2007).
Data source: European Surveillance of Antimicrobial Consumption (ESAC).

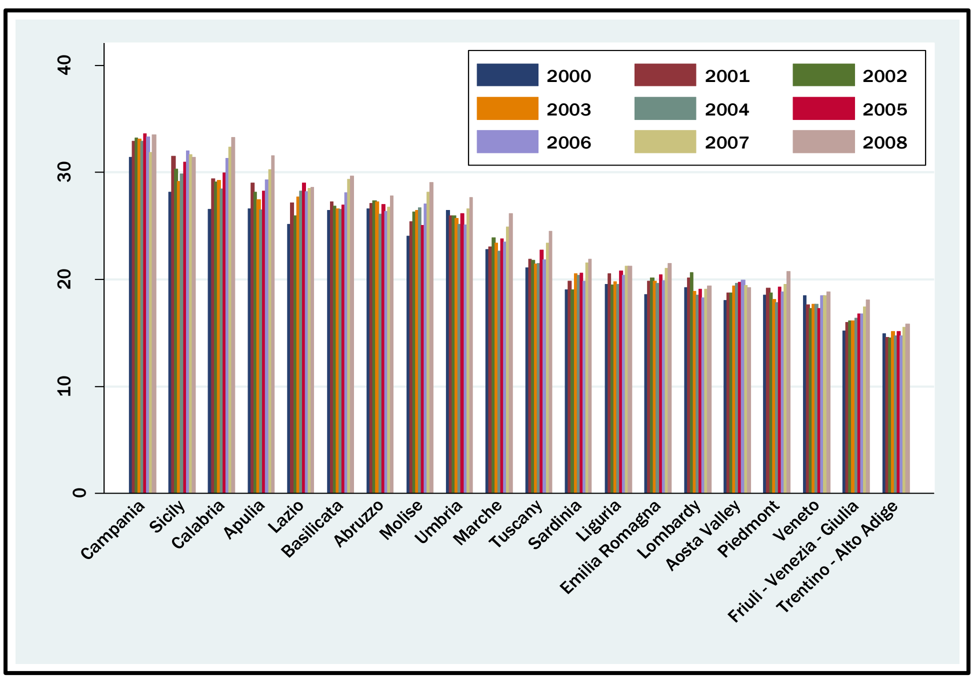

Figure 2: Outpatient antibiotic use in Italy by region (2000-2008)
Data source: Italian National Observatory on Drugs Utilisation (OSMED).

The largest share of consumption is represented by combinations of penicillin with beta-lactamase inhibitor (24.84% in 2007) and broad-spectrum penicillins (21.08% in 2007). Other categories of antimicrobials predominately used in the community are the macrolides (specifically clarithromycin) and quinolones. The structure of consumption has slightly changed over the 9-year period (Figure 3)[5]. The share of combination of penicillin increases from 18.90% in 2000 to 31.33% in 2007. This increase is partially compensated by a decrease in broad-spectrum penicillins, from 22.45% in 2000 to 18.45% in 2007. In this respect, it is worth noting that changes in the use of antibiotic classes are associated to subsequent changes in bacterial resistance. It has been observed that current penicillin resistance depends on the cumulative consumption in the previous two years (Albrich, 2004). The substitution of broad-spectrum penicillins with combination of penicillin with beta-lactamase inhibitors is at least partially explained by the reduced effectiveness of the former category due to increasing bacterial resistance and the availability of a more dynamic subclass of penicillins (Ferech, *et al.*, 2006).

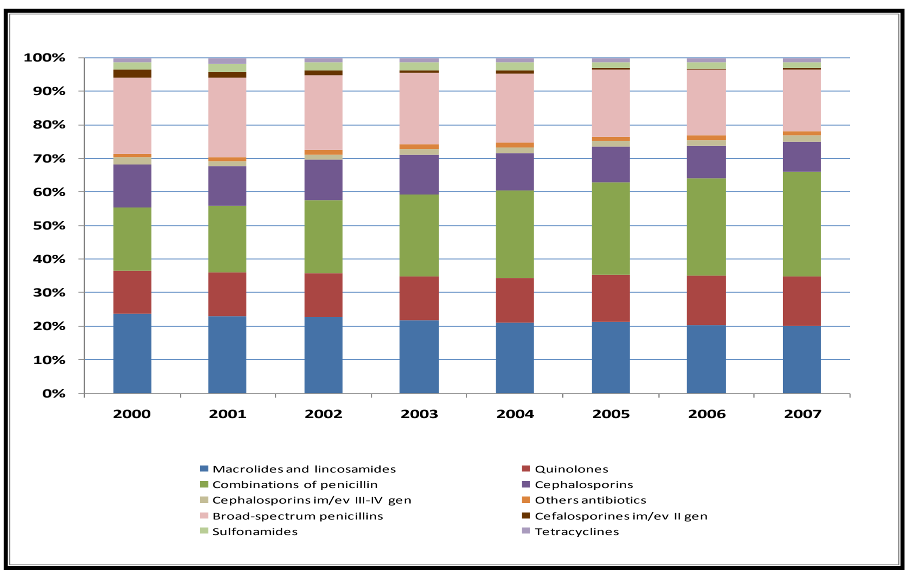

Figure 3: Outpatient antibiotic use in Italy by antibiotic class (2000-2007)
Data source: Italian National Observatory on Drugs Utilisation (OSMED).

[5] We do not report the share of antibiotic use for 2008 because data for all antibiotic classes are not available.

4. Model specification and data

We propose a reduced-form consumption function for outpatient antibiotics,[6] where the variability in antibiotic use among Italian regions depends on socioeconomic characteristics of the population (age structure and income), the supply of health care, individual's health status, and the price (copayment) of antibiotics. Antibiotic consumption in different periods is assumed to be fully separable (Bretteville-Jensen, 2006). This means that current consumption affects consumer's utility in the current period only, without consumer's preferences interactions across time periods.

The following model is specified:

$$DID_{it} = f(Y_{it}, P_{it}, DPH_{it}, POP_{1it}, POP_{2it}, INF_{it}), \qquad (1)$$

where the subscript i denotes the region and t the time period. DID_{it} is antibiotic consumption *per capita*; POP_{1it} is the proportion of the population below 24 and POP_{2it} indicates the proportion of the population older than 64. DPH_{it} is the density of general practices and INF_{it} is the rate of infectious diseases, which is a proxy for individuals' health status. Finally, the model includes income (Y_{it}) and copayment for pharmaceuticals (P_{it}).[7]

For the estimation of equation (1) we use a "hybrid" log-log functional form.[8] The log transformation is applied to income (Y_{it}) and copayment (P_{it}) only since the other covariates are defined as percentage ratios. Equation (1) can then be written as:

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[6] Within the Italian NHS, outpatient antibiotic consumption originates from prescriptions by general practitioners. We hypothesize that the demand for antibiotics registered in the GP's list is defined by the representative general practitioner in the region by taking patients' needs and preferences into account.

[7] There is evidence that income is strongly associated with education and is preferred as a determinant of inequalities in the use of health care services (Habitch *et al.*, 2009).

[8] A linear functional form was also considered. In this case, the results were less satisfactory in terms of goodness of fit and the significance of coefficients.

$$lnDID_{it} = \beta_0 + \beta_1 lnY_{it} + \beta_2 lnP_{it} + \beta_3 DPH_{it} + \beta_4 POP_{1it} + \beta_5 POP_{2it} + \beta_6 INF_{it} + u_{it}. \quad (2)$$

Coefficients β_4 and β_5 capture the effect of the young and the old population, respectively, as compared to the reference population group aged between 25 and 64. u_{it} is an error component with standard normality assumptions.

Our dataset is a balanced panel which includes data for 9 years, from 2000 to 2008, for 20 Italian regions. Summary statistics are reported in Table 2. Data on regional outpatient antibiotic consumption (expenditure) are collected from annual documents prepared by the Italian National Observatory on Drugs Utilization (Osmed). The *per capita* consumption is measured by the number of defined daily doses (DDD) per 1,000 inhabitants per day (DID). A DDD represents the standard dose necessary for one day of drug treatment in adults and is defined by an independent scientific committee answering to the WHO Collaborating Center for Drug Statistics Methodology. The DID measure can be interpreted as the number of persons (out of 1,000) who are taking antibiotics on a given day (Monnet *et al.*, 2004). Dataset comprise sales of antimicrobials - group J of Anatomical Therapeutic Chemical (ATC) classification- included in class A by the Italian NHS (see section 2 above). These drugs require a doctor's prescription and are supplied virtually free of charge, against small patient's copayments. Information on the demographic structure of the population, *per capita* income, density of general practices and rate of infectious diseases are obtained from the Italian National Institute of Statistics (Istat). Copayments are obtained from annual reports on pharmaceutical consumption and expenditure prepared by Osmed. Regional copayments vary from 0 to 4 Euros. We rescale the variable from 1 to 5 in order to avoid negative values in the log transformation.[9]

[9]Adding a positive scalar (*k*) to the values of a covariate (*X*) ensures that the function log (*X*+*k*) is always defined. See Gujarati (1995) for details.

Variable	Variable description	Mean value by year *								
		2000	2001	2002	2003	2004	2005	2006	2007	2008
DID	Defined daily doses per 1,000 inhabitants	22.36	23.37	23.19	23.16	22.96	23.65	23.68	24.37	25.01
		(4.6647)	(5.2823)	(5.2066)	(5.0900)	(5.0702)	(5.2126)	(5.5173)	(5.3457)	(5.5405)
Y	Income *per capita* (in Euro)	20292	21260	21913	22394	23110	23539	24409	25246	25473
		(5203.703)	(5365.841)	(5509.915)	(5634.775)	(5817.211)	(5844.966)	(5893.223)	(6088.59)	(6150.54)
POP_1	Proportion of population aged 0-24	25.58	25.18	24.81	24.50	24.27	24.11	23.99	23.88	23.81
		(4.243)	(4.101)	(3.956)	(3.808)	(3.636)	(3.444)	(3.258)	(3.059)	(2.863)
POP_2	Proportion of population aged 25-64	55.36	55.49	55.58	55.65	55.66	55.57	55.48	55.46	55.46
		(2.357)	(2.276)	(2.189)	(2.088)	(1.961)	(1.818)	(1.649)	(1.468)	(1.309)
POP_3	Proportion of population aged above 64	19.04	19.32	19.59	19.84	20.06	20.30	20.52	20.64	20.71
		(2.920)	(2.895)	(2.877)	(2.869)	(2.837)	(2.768)	(2.702)	(2.641)	(2.559)
DPOP	Population density	174.37	174.42	174.91	176.2	177.82	179.09	180.059	181.273	182.577
		(106.173)	(106.161)	(106.450)	(107.279)	(108.426)	(109.355)	(110.159)	(111.037)	(111.776)
INF	Incidence of infections per 100,000 inhabitants	354.76	316.96	317.70	329.04	302.99	216.25	236.13	213.89	208.76
		(235.915)	(224.020)	(152.282)	(173.007)	(168.503)	(119.663)	(144.240)	(156.629)	(171.408)
DPH	Density of physicians for 1,000 inhabitants	0.8336	0.8292	0.8271	0.8271	0.8224	0.8181	0.8200	0.8220	0.8214
		(0.0624)	(0.0595)	(0.0564)	(0.0595)	(0.0601)	(0.0597)	(0.0597)	(0.0604)	(0.0600)
P	Copayment	1.50	0	0.83	0.85	0.95	0.70	0.65	0.95	1.10
		(0)	(0)	(0.92)	(0.92)	(0.94)	(0.92)	(0.93)	(1.19)	(1.18)

* Standard errors in parenthesis

Table 2: Descriptive statistics.

5. Econometric approach

Two main aspects have to be addressed for a correct approach to the estimation of equation (2): the panel structure of the data and the presence of spatial correlation of antibiotic consumption across regions. As suggested by Baltagi (2005), the use of panel data has some advantages compared to the use of pure time series or cross-sectional data. Panel data allow to control for individual heterogeneity and are more informative. Furthermore, they present more variability and less collinearity, and provide more degrees of freedom and more efficient estimates. Finally, they offer the advantage that units are observed through time and this allows for a simplification of economic aspects that, otherwise, would be more difficult to study.

The temporal dimension pertains to periodic observations of variables characterising cross-sectional units over time. Consequently, two sources of variation are identified: the variation within units over time (within variation) and the variation across units (between variation). These two sources of variation are differently considered by the most widely used econometric approaches to panel data: the pooled ordinary least-squares (OLS) model, the fixed-effects (FE) model and the random-effects (RE) model. Conversely, the spatial aspect pertains to the analysis of the effects of the dependent variable between units (regions). This aspect will be taken into account by means of adequate econometrics estimators included in the above models.

We estimate a FE model, which is a linear regression approach where the intercept term varies cross-sectionally (over the individual units and/or over time). Thus, the common formulation of the model assumes that differences across units can be captured by differences in slopes terms. To test the hypothesis of homogeneity in the constant terms across regions and time periods, we previously run an *F*-test. The large *F*-test statistics suggests that a panel data approach via the FE estimator would give more efficient estimates compared to the pooled OLS approach.

An alternative to the FE approach is the RE model, where the individual term is a stochastic factor, independently and identically distributed across units. The Lagrange multiplier test (Breusch and Pagan, 1979) also indicates that the OLS model can be rejected in favour of the RE model. Moreover, using the Hausman test we verify the hypothesis that the individual-specific error terms are uncorrelated with the explanatory variables, i.e. the RE estimator may be inconsistent. Since the Hausman-test statistics is significant at less than 5% level, we decided to focus on the consistent fixed-effects estimator (see Cameron and Trivedi, 2005, for more details). Note also the relevance of the within variation in most of our covariates.

Concerning the spatial aspect, it is worth noting that regional antibiotic consumption can be affected by individuals' and physicians' attitudes towards antibiotics in adjacent regions. This externality problem can be taken into account by means of adequate spatial econometrics estimators. There are two notable ways to introduce spatial autocorrelation in regression models. These are the spatial-lag model and the spatial-error model. The former refers to a situation where antibiotic consumption in one region is affected by antibiotic consumption in nearby regions. The spatial-lag model is appropriate when there are spillover effects from neighbouring regions. The latter model of spatial dependence focuses on the error term and assumes that error terms in different regions are correlated. This kind of spatial dependence occurs if there are variables that are omitted from the regression model but do have an effect on the dependent variable and are spatially correlated. It is the case, for instance, of random shocks spreading to neighbouring regions.

Both approaches require the specification of a matrix of spatial weights (W). This matrix contains information on the spatial association between observational units. We constructed a contiguity matrix indicating which regions share a border.[10] According to this proximity criterion, the elements of the spatial weight matrix are 1 if location i is adjacent to location j, and zero otherwise. The spatial weights matrix can then be used to test the presence of spatial autocorrelation.

[10] In the case of Sardinia and Sicily the weights were assigned on the basis of the network of maritime routes which links the two islands to the peninsula.

We run two test of spatial autocorrelation: the Moran's *I* (Moran, 1948; Cliff and Ord, 1973; 1981) and Geary's C statistics (Geary, 1954). Moran's *I* statistic is a weighted correlation coefficient formulated as a normalized quadratic form of the variables tested for spatial correlation. Variables are standardised by subtracting the sample mean and then deflated by the variance of the data (Anselin and Bera, 1998). Values range from -1 to +1, where +1 indicates perfect positive correlation, 0 implies no spatial correlation (provided the number of observations is large), and -1 indicates perfect negative correlation. Moran's *I* values can then be transformed to Z-scores for statistical hypothesis testing. The Geary's C statistics gives a value between 0 and 2. The lower value indicates a strong positive spatial autocorrelation. A value of 1 suggests that no spatial autocorrelation is present, whereas negative spatial association is suggested by a value greater than 1 (Goodchild, 1987). This test is inversely related to Moran's *I* but is more sensitive to local rather than global spatial autocorrelation.

The spatial-lag model can be defined as:

$$DID = \rho WDID + X\beta + \varepsilon, \qquad (3)$$

where *DID* is an *N x 1* vector of observations on antibiotic consumption *per capita*, with N= 180; *WDID* is the spatial lag of antibiotic consumption and ρ is the spatial autoregressive parameter; *X* is the *N x k* matrix of explanatory variables, with *k* = 6; β is the vector of regression parameters and ε is a vector of errors.

It is worth noting that spatial dependency is similar to having a lagged-dependent variable as an explanatory variable. The spatial-lag model represents a suitable approach to the study of spatial autocorrelation in antimicrobial consumption since it assumes that antibiotic use is characterised by consumption externalities as suggested by the literature (Fingleton, 2003; Cabrer-Borrás and Serrano-Domingo, 2007). Indeed, antibiotics have a preventive effect since their use may provide external benefits to other individuals, and consequently, reduce the need for consumption in neighbouring areas. However, antibiotics may also produce negative externalities since their utilization may reduce antibiotic effectiveness (increasing bacterial resistance) which may spread to other areas.

As an alternative to the spatial-lag model, one can apply the spatial-error model. This is more relevant when the distribution of residuals in different regions displays spatial correlation. Residual may be spatially correlated if aggregated shocks hit regional health authorities or there are unobservable risk factors concentrated across the areas (Moscone and Knapp, 2005). This effect may be due, for instance, to exogenous bacterial resistance breakdown spreading across the country.

The spatial-error model can be defined as:

$$DID = X\beta + \varepsilon, \tag{4}$$

$$\varepsilon = \lambda W\varepsilon + \mu, \tag{5}$$

where λ is the spatial-autoregressive coefficient and μ is a vector of errors that are assumed to be independently and identically distributed. Note from equation (5) that errors depend on the weighted average of errors in neighbouring regions.

Both spatial approaches have to deal with estimation bias. The multidirectional nature of spatial dependence in the spatial-error model implies that generalized least-squares estimators are inconsistent. The spatial-lag model exhibits endogeneity that can be taken into account by instrumental variables or the general methods of moments techniques, but should preferably be solved using an appropriate maximum likelihood estimator (see Anselin 1988, for details).

In the context of panel data fixed effects can be included in the estimation of equation (3), which leads to a fixed-effects spatial-lag model (SLFE). A maximum likelihood (ML) procedure can be used to estimate the model.[11]Similarly, one can estimate a fixed-effects spatial error-model(SEFE) (see e.g. Elhorst, 2003) using equation (4) and (5). In both models we use the lagged rate of infectious diseases to tackle possible endogeneity related to the health status of the population. Our estimations are carried out using the statistical software Stata (version 11).

6. Results

As suggested above, our initial tests (*F*-test, Lagrange multiplier test, Hausman test) indicate that the OLS model can be rejected in favour of the FE and the RE models. Moreover, the FE approach should be preferred to the RE approach. Table 2 shows the estimation results for the three models (OLS, FE and RE). The results obtained from the two spatial models with fixed effects (SLFE and SEFE) are presented in Table 3. Table 4 summarises the results of the two tests for spatial dependence: the Moran's *I* test and the Geary's C test. In both cases, the null hypothesis is rejected which suggests evidence of spatial autocorrelation in antibiotic use among Italian regions. It is then advisable to extend the FE model to include interdependence of antibiotic consumption across regions by means of spatial models.

Generally, only a few coefficients are significant in all models. Nevertheless, the goodness of fit of our preliminary estimation with OLS is not far from the results of previous analysis of antimicrobial use at regional level.

Overall, the results of the FE and the RE models are similar. The large *F*-test statistics (153.37) suggests that the FE model should be preferred to the OLS model. The Lagrange

[11] The procedure developed by Pisati (2001) to investigate spatially correlated cross-sectional data using maximum likelihood can be easily adapted to estimate a fixed-effects spatial-lag model.

multiplier test also suggests that the OLS model should be rejected (χ^2=212.51) in favour of the RE model. Consequently, we focus on the comparison between the FE and the RE models. The value of the Hausman-test statistics (χ^2 = 55.20) is significant at 5% level and, therefore, we reject the null hypothesis of no correlation between the individual effects and the explanatory variables. Although the FE model should be preferred, in short panels the unknown region-specific effect may not be consistently estimated due to lack of variation over time in some variables, i.e. low within variation (Cameron and Trivedi, 2005). Therefore, we discuss both FE and RE results.

The RE estimation shows a significant impact of age and the rate of mortality for infectious diseases on regional variations in the *per capita* use of antimicrobials. Findings from the FE model also suggest a significant relationship between age and antibiotic consumption. Antibiotic price is significant at 1% level in both the RE and the FE approaches.

Because we use a log-log functional form, we can interpret coefficients as elasticities. In both the RE and FE estimations, income elasticity is positive and highly significant. The result suggests that regions with higher level of income, i.e. northern Italian regions, use more antibiotics compared to lower income regions, *ceteris paribus*. Positive income effects for antimicrobials are also observed by Baye *et al.* (1997) using US data, and by Filippini *et al.* (2009a)using Swiss data. According to the authors, one possible explanation for the low elasticity they found (0.0001) is that the increasing concern over the effects of bacterial resistance from the 1990s may have reduced income elasticity of outpatient antibiotic expenditure over time. Another explanation is that individuals with higher income are more likely to substitute away antibiotics for alternative treatments when income increases.

As expected, copayment has a negative and significant impact on consumption (-0.017 and -0.016). Many studies suggest that copayments are effective in reducing the level of drug consumption of individuals (Freemantle and Bloor, 1996). Using data from Italy, Fiorio and Siciliani (2009) investigate the effect of copayments on the demand for pharmaceuticals. They find that an increase in copayments by €1 reduces the *per capita* number of prescriptions by 4% and the *per capita* public pharmaceutical expenditures by 3.4%. Therefore, the effect of a variation in the level of copayment is not negligible. Our estimates are lower than those found by Contoyannis *et al.* (2005) who investigate exogenous changes in the cost-sharing of prescription drugs in Canada (between -0.12 and -0.16). Own-price elasticities calculated by Rudholm (2003) for three Swedish pharmaceutical submarkets between 1989 and 1996 are also lower (between -0.12 and -3.43).

	OLS Obs: 180 $R^2 = 0.8026$		Random-effects estimator Obs: 180 R^2 overall = 0.0004 Wald $\chi^2 = 63.25^{****}$		Fixed-effects estimator Obs: 180 R^2 overall = 0.4102 F-test = 29.56 ****	
Variables	Coeff.	Std. Err.	Coeff.	Std. Err.	Coeff.	Std. Err.
Constant	- 2.947171 ***	0.985398	0.367176	0.886146	- 2.197376 ***	0.768771
Y	0.199770 ***	0.066077	0.198845 ***	0.080157	0.599471 ****	0.087222
POP_1	0.082505 ****	0.007542	0.012551 **	0.006633	- 0.002991	0.005054
POP_2	0.049781 ****	0.006377	0.014196	0.010256	- 0.033212 **	0.012001
P	- 0.014453	0.015297	- 0.016982 ***	0.008600	- 0.016279 ***	0.006312
DPH	1.427369 ****	0.205754	0.274721	0.186546	0.090184	0.146440
INF_t	- 0.000374 ****	0.000057	- 0.000122 ***	0.000042	- 0.000004	0.000032

* significant at 10%   ** significant at 5%   *** significant at 1%   **** significant at 0.1%

Table 3: Regression results of OLS, RE and FE models.

We estimate the spatial-lag model and the spatial-error model taking unobservable effects into account by means of regional dummies.[12] The estimates of the two models are quite similar (Table 3). Income is highly significant in both models. Antibiotic copayment is significant at a 1% in both models. Contrary to our expectations, the coefficient of the

	Spatial-lag model Obs: 180		**Spatial-error model** Obs: 180	
Variables	**Coeff.**	**Std. Err.**	**Coeff.**	**Std. Err.**
Constant	- 2.751198 ****	0.071420	- 2.662604 ****	0.751848
Y	0.576904 ****	0.083969	0.621709 ****	0.082057
POP_1	- 0.000551	0.004585	- 0.000372	0.005351
POP_2	- 0.032513 ***	0.010757	- 0.029095 ***	0.011106
P	- 0.016277 ***	0.005643	- 0.019600 ***	0.006107
DPH	0.080961	0.133408	0.087320	0.127617
INF_{t-1}	0.000045	0.000029	0.000045	0.000029
Piedmont	- 0.064265	0.039091	- 0.138035 ****	0.031161
Aosta Valley	- 0.221686 ****	0.040594	- 0.304083 ****	0.027357
Lombardy	- 0.230351 ****	0.046447	- 0.312983 ****	0.034342
Trentino-Alto Adige	- 0.528453 ****	0.057942	- 0.604729 ****	0.051016
Veneto	- 0.232358 ****	0.042341	- 0.317992 ****	0.027536
Friuli-Venezia-Giulia	- 0.213381 ****	0.047806	- 0.306720 ****	0.036351
Liguria	0.174853 ***	0.077895	0.094873	0.074698
Emilia Romagna	- 0.086716 ***	0.040426	- 0.161072 ****	0.034623
Tuscany	0.077872 **	0.043794	0.026542	0.041907
Umbria	0.316938 ****	0.051884	0.283986 ****	0.052298
Marche	0.156673 ****	0.040882	0.123859 ***	0.042088
Lazio	0.112236 ****	0.030256	0.091507 ***	0.029134
Abruzzo	0.356418 ****	0.038678	0.348915 ****	0.039691
Molise	0.413152 ****	0.056379	0.428988 ****	0.056020
Campania	0.505710 ****	0.028246	0.539400 ****	0.026980
Apulia	0.407147 ****	0.027452	0.444240 ****	0.024335
Basilicata	0.389027 ****	0.043372	0.421792 ****	0.041529
Calabria	0.500864 ****	0.036811	0.535536 ****	0.035059
Sicily	0.503967 ****	0.035639	0.546108 ****	0.032709
ρ	0.185416 **	0.071420	-	-
λ	-	-	0.253159 ***	0.076898

* significant at 10% ** significant at 5% *** significant at 1% **** significant at 0.1%

Table 3: Regression results of spatial-lag and spatial-error models with fixed effects.

[12] The estimations are performed using the Stata procedure for spatial analysis of cross-sectional data developed by Pisati (2001). To take fixed effects into account, we adapt the procedure by introducing dummy variables for each region.

proportion of people aged above 64 also becomes significant as compared to the FE model. This suggests that older individuals are less likely to use antibiotics compared to adults aged 25-64. According to the literature there is a *U*-shaped relationship between health care spending and age (Di Matteo, 2005). Young and elderly individuals generally use more health services than the mid-age population. We also found that the percentage of population under 25 has a negative impact on antibiotic use, although this effect is not significant.

As for the health status of the population, we observe that once regional dummies are included, the lagged rate of infectious diseases is not significant in both the spatial-lag and spatial-error models.

In order to identify the appropriate form of spatial autocorrelation, we use Lagrange multiplier (LM) tests and their robust versions. The robust LM-lag test and robust LM-error test both suggest the presence of spatial dependency (Table 4). One could argue that the spatial-lag model may be more suitable to our purpose of investigation since the dynamics of the externalities involved (bacterial resistance and prevention from infections) is deterministic rather than similar to random shocks. One result of our analysis is that the spatial lag parameters in the spatial-lag model (ρ) is slightly less significant than the spatial autocorrelation coefficient in the spatial-error model (λ). This may suggest that random shocks related to the dynamics of infections may partially explain spatial interactions between neighbouring areas in the consumption of antibiotics.

Test	Value	p-value
Moran's I	0.77	0.000
Geary's C	0.17	0.000
LM (lag)	36.62	0.000
Robust LM (lag)	32.69	0.000
LM (error)	11.56	0.001
Robust LM (error)	7.63	0.006

Table 4: Results of tests for spatial dependency.

7. Conclusions

Most of the empirical evidence on socioeconomic determinants of antibiotic consumption is based on cross-sectional data and limited to few countries (e.g. Switzerland, Germany, Israel and Hungary). In particular, evident lacks from countries with a National Health Service and substantial decentralization of health care provision to regional health authorities. The cross-sectional approach has some drawbacks such as the inability to solve the problem of omitted variables. This is even more relevant when only limited data are available for important factors, such as bacterial resistance to antimicrobials. A further limitation is represented by the need to impose full regional homogeneity in the parameters of the random process that describes the use of antibiotics. To overcome these problems, we analysed socioeconomic determinants of antibiotic consumption by means of panel data from a new country (Italy).

The consumption of antibiotics cannot be regarded as independently generated within regions because of possible spillover effects. Antibiotics may reduce the risk of infections in neighbouring areas (positive externality) and may reduce the effectiveness of treatment because of bacterial resistance spreading (negative externality). As a consequence, standard estimation procedures employed in many empirical studies can lead to serious bias and inefficiency in the estimates. Our approach allowed to consider spatial effects across regions. We captured these effects by means of a spatial-lag model and a spatial-error model.

We found significant and positive income elasticity and negative effects of copayments. Antibiotic use is also affected by the demographic structure and the health status of the population. Finally, we found evidence of spatial autocorrelation in the use of antibiotics across Italian regions. This suggests that regional policies (e.g. public campaigns) aimed at increasing efficiency in antibiotic consumption and controlling bacterial resistance may not be independent and could be influenced by policy makers in neighbouring regions. There will be scope for a strategic and coordinated view of regional policies towards the use of antibiotics.

References

Albricht WC *et al.* (2004) Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes. Emerging Infectious Diseases* 10: 514-517

Anselin L (1988) Spatial econometrics: Methods and models. Dordrecht, the Netherlands: Kluwer

Anselin L and Bera A(1998) Spatial dependence in linear regression models with an introduction to spatial econometrics. In: A. Ullah and D.E.A. Giles, Eds., *Handbook of Applied Economic Statistics*, 237-289

Atella V *et al.* (2003) Cost to the patient or cost to the healthcare system? Which one matters the most for GP prescribing decisions? A UK-Italy comparison, CEIS Tor Vergata Research Papers No. 1

Baltagi B (2005) Econometric analysis of panel data. Third edition, Willey

Baye MR *et al.* (1997) Demand systems and the true sub-index of the cost of living for pharmaceuticals. *Applied Economics* 29: 1179–1189.

Bretteville-Jensen AL (2006) Drug demand – initiation, continuation and quitting – *De Economist* 154: 491-516

Breusch T and Pagan A. (1979) A simple test of heteroskedasticity and random coefficient variation. *Econometrica* 47: 1287-1294

Cabrer-Borrás B and Serrano-Domingo G (2007) Innovation and R&D spillover effects in Spanish regions: A spatial approach. *Research Policy* 36: 1357-1371

Cameron A and Trivedi P (2005) Microeconometrics. Methods and Applications. Cambridge University Press, Cambridge

Cliff A and Ord J (1973) Spatial Autocorrelation. Pion, London

Cliff AD and Ord JK (1981) Spatial Processes: Models and Applications. Pion, London

Contoyannis P *et al.* (2005) Estimating the price elasticity of expenditure for prescription drugs in the presence of non-linear price schedules: an illustration from Quebec, Canada. *Health Economics* 14: 909-923

Costa-Font J, Kanavos P, and Rovira J (2007) Determinants of out-of-pocket pharmaceutical expenditure and access to drugs in Catalonia. *Applied Economics* 39: 541-551

Di Matteo L (2005) The macro determinants of health expenditure in the United States and Canada: assessing the impact of income, age distribution and time. *Health Policy* 71: 23-42

ElhorstJ (2003) Specification and estimation of spatial panel data models. *International Regional Science Review* 26: 244-68

Elseviers M *et al*. (2007) Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations. *Pharmacoepidemiologyand Drug Safety* 16: 115-123

European Commission (2010) Antimicrobial Resistance. *Eurobarometer* 338/Wave 72.5 – TNS Opinion & Social, Luxembourg

Ferech M *et al*. (2006) European Surveillance of Antimicrobial Consumption (ESAC): outpatient penicillin use in Europe, *Journal of Antimicrobial Chemotherapy* 58(2): 408-412

Filippini M, Masiero G, and Moschetti K(2006) Socioeconomic determinants of regional differences in outpatient consumption: Evidence from Switzerland, *Health Policy* 78: 77-92.

Filippini M, Masiero G, and Moschetti K (2009a) Small area variations and welfare loss in the use of outpatient antibiotics. *Health Economics, Policy and Low* 4: 55-77

Filippini M, Masiero G, and Moschetti K (2009b) Regional consumption of antibiotics: a demand system approach. *Economic Modelling* 26: 1389-1397

Fingleton B (2003) Externalities, economic geography, and spatial econometrics: conceptual and modeling developments, *International Regional Science Review* 26: 197-207

Fiorio C and Siciliani L (2010) Co-payments and the demand for pharmaceuticals: Evidence from Italy. *Economic Modelling* 27(4): 835-841

Freemantle N and Bloor K (1996) Lessons from international experience in controlling pharmaceutical expenditure I: influencing patients. *British Medical Journal* 312: 1469-1471

Geary R (1954) The contiguity ratio and statistical mapping. *The Incorporated Statistician* 5: 115-145

Goodchild MF (1987) A spatial analytical perspective on geographical information systems. *International Journal of Geographical Information Systems* 1: 327-334

Gujarati D (1995) Basic econometrics. Third edition McGraw-Hill (New York)

Huttner B, Goossens H, Verheij T, Harbarth S, on behalf of the CHAMP consortium (2010) Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *The Lancet Infectious Diseases* 10:17–31

Kern WV *et al*. (2006) Regional variation in outpatient antibiotic prescribing in Germany. *Infection* 34(5): 269-273

Matuz M *et al*. (2005) Regional variations in community consumption of antibiotics in Hungary, 1996-2003. *British Journal of Clinical Pharmacology* 61(1), 96-100

Mera RM, Miller LA, and White A (2006) Antibacterial use and *Streptococcus pneumoniae* penicillin resistance: a temporal relationship model. *Microbial Drug Resistance* 12: 158-163

Monnet DL *et al* (2004) Defined daily doses of antimicrobials reflect antimicrobial prescriptions in ambulatory care. *Journal of Antimicrobial Chemotherapy* 53: 1109-1111

Monroe S and Polk R (2000) Antimicrobial use and bacterial resistance. *Current Opinion in Microbiology* 3: 496-501.

Moran P (1948) The interpretation of statistical maps. *Journal of the Royal Statistical Society* Series B10: 243-251

Moscone F and Knapp M (2005) Exploring the spatial pattern of mental health expenditure. *Journal of Mental Health Policy and Economics* 8: 205-217

Nitzan *et al*. (2010) Variability in outpatient antimicrobial consumption in Israel, *Infection* 38: 12-18

Pisati M (2001) Tools for spatial data analysis, Stata Technical Bulletin stb-60

Revelli F (2001) Spatial patterns in local taxation: tax mimicking or error mimicking? *Applied Economics* 33: 1101-1107

Rudholm N (2003) Competition and substitutability in the Swedish pharmaceuticals market. *Applied Economics* 35: 1609-1617

Estimating dynamic consumption of antibiotics using panel data: the shadow effect of bacterial resistance

1. Introduction

The raising use of antibiotics and the associated adverse effects of bacterial resistance have become a growing concern worldwide. Scientific evidence strongly supports the relationship between antimicrobial use and resistance to antibiotics. Hence, control over antibiotic use may reverse bacterial resistance (Cizman, 2003).

It has been shown that the potential welfare loss due to bacterial resistance may account for up to 12% of total outpatient antibiotic expenditure (Filippini *et al.*, 2009a). Although public interventions may be effective in controlling antibiotic consumption (Huttner *et al.*, 2010), the effects of intervention policies on resistance to antimicrobial drugs cannot be assessed accurately at present. The consumption dynamics of antibiotics and its behavioural aspects are still unclear.

To some extent, antibiotics are similar to addictive goods since individuals may develop dependence or experience persistent attitudes towards consumption. Addiction is a negative side-effect of consumption where the characteristics of goods interact with the characteristics of individuals. Consumption of addictive goods is characterized by reinforcement (higher levels of consumption in the past increases the desire for present consumption) and tolerance (utility of a given level of consumption is lower when past consumption is higher) (Peper, 2004). In the case of antibiotics, current consumption may be affected by past consumption because of endogenous bacterial resistance. Past consumption increases bacterial resistance, i.e the "capital stock", which in turn reduces the effectiveness of antibiotic use over time (Laxminarayan and Brown, 2001; Herrmann and Gaudet, 2009).

To ourknowledge, the study of antibiotic consumption is limited to the investigation of cross-sectional data (Kern *et al*., 2006; Filippini *et al*., 2006). However, as suggested above, dynamic aspects of consumption may play an important role since the spread of antimicrobial resistance reduces antibiotic effectiveness on each individual as well as for other individuals in the community (external effects) and could be related to behavioural factors. The mechanism of transmission of antimicrobial resistance can be described by the basic SIS epidemiological model (Wilen and Msangi, 2003). The model hypothesises that the population is partitioned into infected individuals and individuals in good health. Uninfected individuals may become infected through contact with the infected population which includes individuals infected with a drug-resistant strain. Drug-resistant strains can then be transmitted to healthy individuals according to the number and the speed of contacts among individuals. Some individuals infected with a drug-resistant strain naturally recover, but the rate of recovery for those treated with antibiotics remains unchanged. Consequently, the spread of bacterial resistance also depends on the biological cost for the resistant strain. Although in the absence of treatment the resistant strain clears at a faster rate than the strain susceptible to antibiotics, it survives to antibiotic treatment. Fast and numerous contact among individuals and the large use of antibiotics favour the resistance strain, thus leading to an increase in the overall level (stock) of bacterial resistance in the community. From the empirical point of view, we should note that data on the "capital stock", i.e. the level of bacterial resistance, are unfortunately not usually available.

Econometric models may incorporate the influence of consumption habits on preferences over time (Spinnewyn, 1981). To include habits or addiction aspects in models of antibiotic consumption one can drop the assumption that an increase in current consumption has just an impact on current individual's utility and assume correlation between consumption and utility in subsequent periods. Indeed, this is the case if antibiotics are an exhaustible resource since their efficacy may be reduced by endogenous bacterial resistance.

Plausibly, individuals (and their doctors) are myopic in the sense that the effects of present antibiotic consumption on future consumption are not taken into account in their consumption choices. Past consumption is supposed to affect present consumption only through the reduced level of antibiotic effectiveness. Past antibiotic consumption can either be taken into account by means of lagged or stock variables included in empirical models of consumption. Lagged variables have been considered, for instance, in Baltagi and Levin (1986), to estimate the demand for cigarettes, and by Johnson and Oskanen (1977) to study the demand for alcohol (Bretteville-Jensen, 2006). Since in our case information on the capital "bad", i.e. the stock of bacterial resistance, is not available, we follow the lagged variable approach.

The purpose of this article is to explore how consumers adjust their current level of antibiotic consumption towards desired levels over time. We propose a dynamic approach to capture the partial adjustment in consumption and the speed of adjustment. We estimate a model of antibiotic consumption using a balanced panel of outpatient antibiotic use and several socioeconomic determinants in 20 Italian regions between 2000 and 2008. Estimations are carried out by means of two suitable approaches for short dynamic panels: the bias-corrected least squares dummy variable (LSDVC) dynamic panel estimator proposed by Kiviet (1995) to reduce the small sample bias associated to the least squares dummy variables estimator, and the generalized method of moments proposed by Blundell and Bond (1998) (GMM-BB).

Most of our findings on the impact of determinants of consumption will prove consistent with previous results of static models of antibiotic use. In addition, we show that past antimicrobial use affects current consumption and the adjustment towards desired levels of consumption is relatively fast. This may indicate that individuals are responsive to changes in antibiotic inefficacy (bacterial resistance).

The remaining of the paper is organized as follows. Section 2 provides an overview of the three main fields of the literature which are most closely related to our paper: the empirical analysis of the determinants of antibiotic consumption, the theoretical literature on optimal antibiotic consumption, and the empirical literature on addictive goods and habit formation. In Sections 3 and 4 we sketch the model and discuss the estimation approach. Section 5 presents the results and Section 6 concludes.

2. Review of the literature

The literature is relatively rich of studies investigating socioeconomic determinants of antibiotic consumption in outpatients within countries. Nitzan *et al.* (2010), for instance, analyse the use of antibiotics in outpatients by different age groups in 8 districts of Israel. Filippini *et al.* (2006) propose an econometric model where antibiotic use across Swiss regions varies according to the socioeconomic and demographic characteristics of the population, the incidence of infections, the local supply of health care and antibiotic price. Kern *et al.* (2006) investigate variations in antibiotic prescriptions across 23 areas in 16 German states in relation to age, population density, income, unemployment, and aspects of local health care supply. Finally, Matuz *et al.* (2005) explore regional variations in antibiotic consumption in ambulatory care in Hungary.

The above studies exploit cross-sectional data. To our knowledge, the literature lacks econometric studies on determinants of outpatient antibiotic consumption using panel data. In a companion paper, weexplore variations of antibiotic use across Italian regions using panel data. The modelling approach is based on ordinary least squares with fixed and random effects. Spatial econometric tools are also applied to count for the fact that antibiotic consumption may be affected by antimicrobial use in neighbouring regions. However, dynamic aspects of consumption are not considered.

Static models of antibiotic consumption ignore the link between consumer's preferences in different time periods and assume that an increase in current consumption affects utility in the current period only (Bretteville-Jensen, 2006). Consequently, consumption in different periods is fully separable, which implies that individuals are assumed to instantaneously adjust to the optimal level of consumption. However, this may not be very realistic and the reasons will be carefully discussed in the following section.

The literature on dynamic aspects of consumption can be divided in two main fields (Chaloupka, 1991). The first one is represented by studies on endogenous tastes or habit formation (see e.g. Gorman, 1967; Pollak, 1970, 1976; and Boyer, 1983). The second one consists of studies on rational addictive consumption (Stigler and Becker, 1977; Becker and Murphy, 1988; Becker *et al*, 1991, 1994). The main insights of rational addiction are theoretically derived by Becker and Murphy (1988), who show that addictive behaviour is influenced by the discount rate of future consumption, expected income and the price changes. Moreover, the long-run demand for addictive goods tend to be more elastic than the demand for non-addictive goods because their consumption at different moments of time are complements. Many empirical studies which follow this seminal work focus on the comparison between myopic and rational addictive behaviour. Tiezzi (2005), for instance, investigates the demand for tobacco in Italy using a balanced pseudo-panel of annual data on tobacco and related products during the period 1972-2000 for the 20 Italian regions and time series data on *per capita* household tobacco expenditures during the period 1960-2002 by means of myopic and rational models of addiction. Similarly, Luo *et al.* (2003) investigate cigarette consumption in Japan using time-series data covering from 1960 to 2000.

As for antibiotics, two main aspects influence their consumption over time. First, antibiotics have the characteristics of preventive care. In this sense the use of antibiotics may contribute to reduce the spread of bacterial infections to other individuals, which may increase future benefits from consumption. Second, current antibiotic use increases the stock of bacterial resistance which in turn reduces the effectiveness of antibiotics over time.

The literature generally models bacterial resistance as a negative externality since the risk of transmission of bacterial resistance affects the welfare of the population (Rudholm, 2002; Elbasha, 2003). This externality depends, at least partially, upon the quantity of antimicrobials consumed (Coast *et al.*, 1998). Antibiotic resistance generates additional costs in the form of increased hospitalizations, higher mortality rates, and the diversion of resources from other medical needs into the development of new and more powerful antibiotics (Laxminarayan, 2001). Hence, the full cost of antibiotic treatment includes the monetary cost as well as the additional cost of reduced effectiveness due to past consumption. These costs should balance the expected benefits from antibiotic treatment at least in the long run when information is fully available to the consumers. However, the literature suggests that consumers (and their doctors) are rather myopic when using antibiotics. Indeed, several factors may contribute to increase antibiotic consumption, which in turn reduces antibiotic effectiveness over time.

Many theoretical studies address the issue of optimal consumption of antimicrobials. Laxminarayan and Weitzman (2002) argue that most patients in region or country are treated with the same drug for a given infectious disease, which places high selection pressure on organisms that are susceptible to that particular drug and increases the likelihood that a resistant strain will evolve and spread. As resistance to the recommended fist-line drug builds up, that drug is replaced by an alternative that is used until resistance to the second drug also increases, and so on in succession. The authors concludes that this myopic strategy is not optimal and should be replace by the simultaneous prescription of a variety of drugs.

Rudholm (2002) suggests that the use of antibiotics in one region creates a stock of resistant bacteria which affects the welfare of consumers in other regions. Since consumers do not take this effect into account when choosing the level of antimicrobial consumption, this may result in a suboptimal allocation of resources at the global level.

Herrmann and Gaudet (2009) analyse the exploitation of an antibiotic in a market subject to open access on the part of antibiotic producers to the common pool of antibiotic efficacy. While the market equilibrium depends only on current levels of antibiotic efficacy and infection of the epidemiological system, the social optimum accounts for the dynamic externalities which relate those levels to the inter-temporal use being made of the antibiotic. They explicitly derived a demand function for the antibiotic under the assumption that individuals differ with respect to their valuation of being in good health. Furthermore, the authors show that in the open-access equilibrium, the level of antibiotic efficacy tends to a positive steady-state level in which the efficacy renews itself so as to maintain the steady state. It turns out that this steady-state level of antibiotic efficacy can be lower or higher than the level which should prevail in the socially optimal steady state.

Finally, several empirical studies support the idea that there is limited rationality in antibiotic consumption. Antibiotic prescriptions, for instance, represent a mean of shortening doctor's consultation since there is little time for clinical investigations to exclude other diagnosis. Moreover, prescribers may be concerned with the risk of losing patients and the perception of poor outcome if antibiotics are not prescribed (Sachs and Tomson, 1992). Physicians may also fear legal consequences if they fail to secure an adequate treatment. Prescribing may then contribute to relieving doctor's anxiety.

Uncertainty in the diagnosis and limitation in the follow up of patients provides an additional concern. This generates a preference for antibiotics with a broad spectrum to cover the broader range of bacteria. To conclude, the cost of diagnostic tools makes it difficult to persuade the patient that antibiotic treatment is not needed (Nordberg *et al.*, 2005).

3. The model

In this section we sketch a dynamic model of antibiotic consumption in outpatient care where consumers' rationality is limited by poor information available on the future costs of antibiotic effectiveness (bacterial resistance). The model builds on previous approaches to habit formation and addictive goods (e.g. Becker and Murphy, 1988). Two main aspects can be considered. First, greater past consumption of antibiotics increases the desire for present consumption. This represents the so called *reinforcement effect* and indicates that individuals who undergone antibiotic treatment in the past are more likely to consider the use of antibiotics in the current period.[13] Second, the utility of a given amount of antibiotics (standard doses of therapy) is lower when past consumption is greater. This is because of endogenous bacterial resistance which reduces antibiotic efficacy over time. To be cured, a patient will need more antibiotics since more therapies have to be considered before finding the effective one and cure the infection.[14] Third, there is an optimal stock

[13] This may be explained by some physical or psychological effects which persist over time. It may also reflect physician's attitude toward antibiotic prescriptions. Under uncertainty on the nature of patient's infection, antibiotic therapy may appear to have been beneficial even though patient's relief was not due to the treatment. General practitioners may prefer antibiotic therapies since they were presumably effective in the past or patients are not willing to wait for recovery.

[14] Under uncertainty on antibiotic effectiveness (levels of bacterial resistance), doctors usually start with the traditional therapy and then move to new antibiotic therapies when the former proved ineffective. This implies that the total amount of antibiotic doses will increase.

of bacterial resistance which depends on individual antibiotic consumption as well as consumption of other individuals.[15]

Rational individuals weigh the present benefit of antibiotic consumption against the future health consequences in terms of the risk of antibiotic inefficacy and the future costs of purchasing new pharmaceutical drugs. However, patients and their doctors are not fully aware of the future harmful consequences of current antibiotic consumption. The rational is that the mechanism that generates antibiotic resistance from past antibiotic consumption is quite complex and the spreading process to different antimicrobial categories is not well understood. Doctors have limited information on levels of antimicrobial resistance and patients may not be able to evaluate correctly the impact of resistance on future antibiotic efficacy. Moreover, the future costs of pharmaceutical innovation are not taken into account. Patients bear a small fraction of the full cost of antibiotics directly because of social health insurance coverage. Furthermore, the decision to request an antibiotic is based on two factors: the benefit of quickly recovering from an infection and the cost of taking the medication. But patients may not be aware of studies that have demonstrated conclusively that prior use of antibiotics increases a person's risk of acquiring a resistance infection (Laxminarayan, 2001). Finally, current antibiotic inefficacy may also be generated by past antibiotic consumption of other individuals. This implies that the stock of bacterial resistance has an externality effect which is not considered in individual's utility maximizing choices.

We hypothesise that the utility of a representative individual in region i depends on the consumption of a composite good, $c_i(t)$, the consumption of antibiotics measured by the amount of standard defined daily doses, $DID_i(t)$, and on a measure of past consumption

[15] From a biological perspective, individuals may experience a level of bacterial resistance which is positive or zero. This level depends on the individual consumption as well as the consumption of other individuals. Since the use of antibiotics generates expected benefits (infection cured) and costs (antibiotic inefficacy and monetary costs), individuals should try to optimise their level of consumption, i.e. to reach the optimal stock of bacterial resistance.

which captures the level of inefficacy of antibiotics, i.e. the stock of bacterial resistance, $R_i(t)$. The latter measure draws from the classical "SIS" model used in epidemiological studies (Lindquist *et al.*, 2010). This defines antibiotic inefficacy as $R_i(t) = I_i^R(t)/I_i(t)$, where $I_i^R(t)$ represents the number of individuals infected with a drug-resistant strain and $I_i(t)$ is the total number of infected individuals in the population. The variation in antibiotic efficacy over time, $\partial R_i(t)/\partial t$, is supposed to depend on individuals treated, n_i, and on the fitness cost of resistance, δ. The latter is a measure of the rate at which bacteria regress to the susceptibility state in the absence of antibiotic treatment. We can interpret this process as the depreciation rate of the stock of bacterial resistance. We then assume the following relationship:

$$\frac{\partial R_i(t)}{\partial t} = \beta \sum_{j=1}^{n_i} DID_j\,(t) - \delta R_i(t). \qquad (1)$$

From an economic point of view, the optimal use of antibiotics depends on whether drugs are a renewable resource. This is related to the depreciation rate of the stock of bacterial resistance, δ. If resistant bacteria were less likely to survive in the absence of antibiotics, one could consider to remove an antibiotic temporarily from active use to enable it to recover its effectiveness. On the other hand, if the resistant strain remains prevalent, then an antibiotic would fail to regain its effectiveness even if it were temporarily removed. Effectiveness would be treated as a non-renewable or exhaustible resource. This would imply higher costs for pharmaceutical innovation to replace the ineffective treatment unless the exhaustible resource was used more carefully.

Note that antibiotic inefficacy is a function of past consumption of all individuals in the region. There is a externality effect represented by the efficacy constraint generated by antibiotic consumption of other individuals in the region. However, we hypothesise that bacterial resistance cannot be transferred to individuals in other regions.[16]

Assuming that individuals in region i are identical, with a length of life equal to T and a constant rate of time preference, σ, we can write the utility function:

$$U_i(0) = \int_0^T e^{-\sigma t} u_i[c_i(t),\ DID_i\,(t),\ R_i(t)\,]dt, \quad (2)$$

subject to an expenditure constraint which depends upon the price of antibiotics and other goods, earnings over time and the discount rate. Individuals maximise utility in (2) taking the expenditure constraint and the investment equation (1) into account (see Becker and Murphy, 1988, for details). A stable equilibrium is depicted in Figure 1 where DID^* and R^* represent optimal levels of antibiotic consumption and stock of bacterial resistance.

As shown in Figure 1, the long-run level of antibiotic consumption is fully adjusted to its equilibrium level. At any point in time, however, current antibiotic consumption differs from the long-run equilibrium consumption. This may be imputed to the fact that consumers are not well informed about levels of bacterial resistance in their area. Nevertheless, bacterial resistance represents a constraint on antibiotic utilisation. Consequently, a link between antibiotic consumption in different periods is plausible. However, while past consumption is supposed to affect present consumption, it seems plausible to assume that individuals are myopic when choosing antibiotic treatment and the possible effects of present consumption on future consumption are not taken into account.

[16] Bacterial resistance generated by individual consumption represents an efficacy constraint for other individuals. It is plausible to assume that bacterial resistance spreads within the region, i.e. it is a local phenomenon. However, researchers have hypothesized that bacterial resistance may have global effects (Rudholm, 2002). Spatial aspects have been considered in two previous papers using cross-sectional data (Filippini *et al.*, 2009a, 2009b).

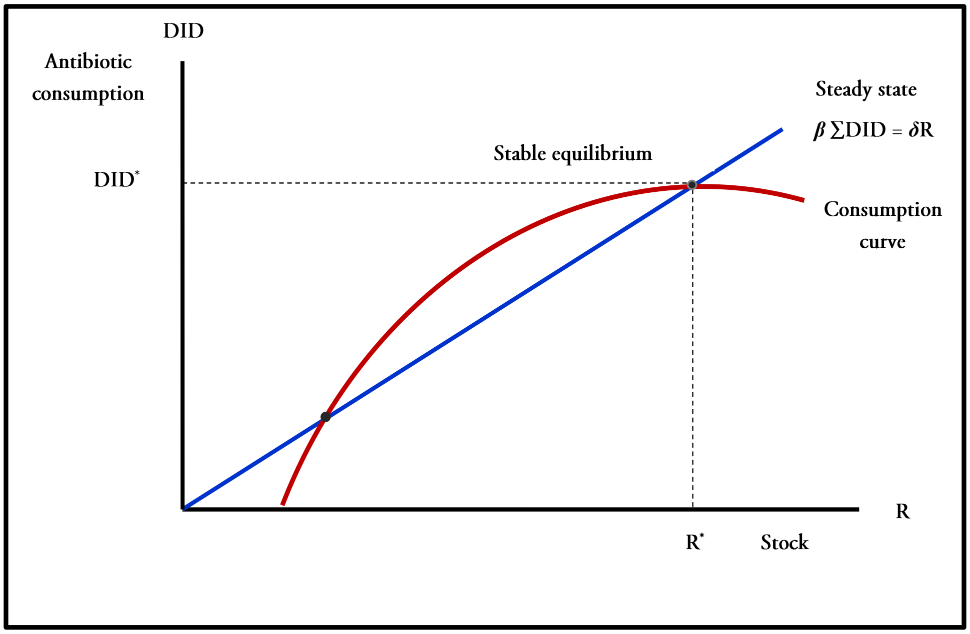

Figure 1: Model of (limited) rational antibiotic consumption. Resistance (capital) stock "reinforces" antibiotic consumption since past antibiotic treatment increases preferences for present treatment and the efficacy from a given treatment is lower when past consumption is greater (tolerance).

Due to the fact that we are not able to observe the stock of bacterial resistance directly, the empirical approach presented here is based on the idea that antibiotic consumption follows a partial adjustment process where the lagged dependent variable represents a fixed propensity to consumption which is carried over from period to period. The coefficient of the lagged variable can be interpreted as the speed of the adjustment to the steady state level of consumption (Tiezzi, 2005). Hence, current antibiotic use, DID_t, differs from optimal use, DID^*_t, because the adjustment to optimal levels is not immediate.

In this framework the relationship between current and desired levels of antibiotic consumption can be summarised as:

$$lnDID_{it} - lnDID_{it-1} = \varphi \left(lnDID^*{}_{it} - lnDID_{it-1} \right) + \eta_{it}, \qquad (3)$$

where η_t is a random disturbance term and φ is the coefficient of adjustment indicating the rate of movement towards the desired level of consumption. It is worth pointing out that for φ=1 the adjustment to desired levels of antibiotic consumption is instantaneous. Conversely, for φ=0 there is no adjustment. Thus, we hypothesise that $0 < \varphi \leq 1$.

Solving (3) for the optimal level of consumption we get:

$$lnDID_{it}^{*} = \frac{1}{\varphi} lnDID_{it} + \left(1 - \frac{1}{\varphi}\right) lnDID_{it-1} - \frac{1}{\varphi}\eta_{it}, \tag{4}$$

Since the desired level of consumption DID^{*}_{it} cannot be observed, equation (4) reformulates the unobserved DID^{*}_{t} in terms of the observed levels of DID_t and DID_{t-1}, as well as the unobserved parameter φ and the random disturbance term η_{it} .

To empirically investigate the dynamics of antibiotic use we hypothesise that regional consumption within a country depends on socioeconomic characteristics of the population characteristics (income and age structure), the local supply of health care, the prevalence of community-acquired infections, and antibiotic price or copayment.

Let the optimal level of antibiotic use in region *i* at time *t*, measured in defined daily doses per 1,000 inhabitants, be described by the following reduced form equation:

$$\begin{aligned} lnDID_{it}^{*} = {} & \beta_0 + \beta_1 lnY_{it} + \beta_2 lnP_{it} + \beta_3 DPH_{it} + \beta_4 POP_{1it} + \beta_5 POP_{2it} + \\ & \beta_6 INF_{it} + \beta_7 DPOP_{it} + \beta_8 NORTH + \beta_9 CENTER + \varepsilon_{it}, \end{aligned} \tag{5}$$

In the hybrid log-log functional form of equation (5) P_{it} is antibiotic price/copayment, DPH_{it} is the density of physician practices, POP_{1it} is the proportion of the population below 24 and POP_{2it} indicates the proportion of the population older than 64. INF_{it} is the rate of infectious diseases, and $DPOP_{it}$ is population density. The log transformation is applied only to income and price since other variables are defined as percentage ratios. Two dummy variables (NORTH and CENTER) are also included to capture geographical differences between northern, southern and central regions.

Substituting the right-hand side of equation (5) for $lnDID^{*}_{it}$ in (4) and rearranging we obtain:

$$lnDID_{it} = \beta_0\varphi + (1-\varphi)\, lnDID_{it-1} + \beta_1\varphi lnY_{it} + \beta_2\varphi lnP_{it} + \beta_3\varphi PDH_{it} + \beta_4\varphi POP_{1it} + \beta_5\varphi POP_{2it} + \beta_6\varphi INF_{it} + \beta_7\,\varphi DPOP_{it} + \beta_8\,\varphi NORTH + \beta_9\,\varphi CENTER + v_{it}, \quad (6)$$

where (1 - φ)represents the speed at which individuals achieve the desired level of consumption and the composite disturbance term is $v_{it} = \varphi\varepsilon_{it} + \eta_{it}$. The model derived in (6) can be estimated by means of appropriate econometric techniques discussed in the following section.

4. Econometric approach and data

For the estimation of the dynamic model in (6) we have a balanced panel dataset for the 20 Italian regions. To account for unobserved heterogeneity in panel data, we could use a fixed effects (LSDV) or random effects (RE) model. However, the estimation of the dynamic panel data model (6) using LSDV or RE estimators is not appropriate. This is because the inclusion of lagged dependent variables among explanatory variables violates the strict exogeneity assumption. In fact, the lagged variable is correlated with the error term, which leads to biased and inconsistent estimates of LSDV and RE.[17] In the literature several instrumental variable estimators have been proposed to solve this problem. Anderson and Hsiao (1982) proposed a simple instrumental variable estimator. Arellano and Bond (1991) as well as Blundell and Bond (1998) proposed two different estimators

[17] For a discussion of this issue and for a presentation of econometric models for panel data see Baltagi, 2002.

based on the general method of moments (GMM). The basic idea of these estimators is that lagged levels and/or additionally lagged differences are valid instruments for the lagged endogenous variable, that is they are uncorrelated with the transformed error term.

The Arellano and Bond estimator (GMM-AB) has the advantage of producing consistent estimates in dynamic panel regression with both endogenous right-hand side variables and measurement errors. Moreover, it is more efficient than the standard Instrumental Variables (IV) estimators such as the Anderson-Hsiao estimator. Nevertheless, the method is unlikely to be suitable for small samples. It has been shown that, when T is small and the parameter of the lagged variable is close to one, then the GMM-AB estimator can be biased downward. As an alternative to the approach suggested by Arellano and Bond (1991), Blundell–Bond (1998) proposed a system GMM estimator (GMM-BB) which uses lagged first differences as instruments for equations in levels as well as the lagged variable in first-difference equations. Blundell-Bond (1998) showed that this estimator seems to be preferable to other IV and GMM estimators with small samples. A problem with this estimator is that properties hold for N large, so the estimation results can be biased in panel data with a small number of cross-sectional units.

An alternative econometric approach for small dynamic panel data set based on the correction of the bias of LSDV has been suggested by Kiviet (1995). To make the correction feasible, this procedure has to be initialized by a consistent estimator. This is because the bias approximation depends on the unknown population parameters. Three possible options to reach this purpose are the Anderson-Hsiao, the Arellano-Bond, and the Blundell-Bond estimators. Finally, the estimated asymptotic standard errors may provide poor approximations in small samples, generating unreliable t-statistics. Bootstrap methods generally provide approximations to the sampling distributions of statistics, which are at least as accurate as approximations based upon the first order asymptotic assumptions.

In a Monte Carlo analysis, Judson and Owen (1999) and Kiviet (1995) showed that in typical aggregate dynamic panels characterized by T lower or equal to 20 and N lower or equal to 50, as it is our case, the Anderson-Hsiao and the Kiviet corrected LSDV (LSDVC) estimators are better than the GMM estimator proposed by Arellano and Bond (1991). Despite having a higher average bias, the corrected LSDV estimator turns out to be more efficient than the Anderson-Hsiao. This suggests that the corrected LSDV estimator is an effective approach for small panels ($T \leq 20$), while the Anderson-Hsiao estimator is more appropriate for large panels, as the efficiency of the latter improves with T (Kiviet, 1995).

Our regional panel includes 20 regions for the period 2000-2008. Hence, the GMM-AB estimator may not be the most appropriate approach. Given the characteristics of our panel, wechoose to estimate the dynamic model (6) using the following two estimators: one-step system GMM estimator proposed by Blundell and Bond (1998) and the LSDVC.[18]

The balanced panel dataset for the 20 Italian regions has been created using several sources. Data on regional outpatient antibiotic consumption were collected from annual reports prepared by the Italian National Observatory on Drugs Utilization (Osmed). The dataset includes sales of antimicrobials, i.e. group J of the Anatomical Therapeutic Chemical Classification (ATC) of drugs. These drugs are included in class A by the Italian National Health Service (SSN), which means they require a doctor's prescription and are supplied virtually free of charge, against small patient's copayments. The *per capita*

[18] Spatial aspects of consumption are not considered here. These aspects are addressed in studies using cross-sectional data (Filippini *et al.*, 2009a, 2009b) and in a companion paper (González and Masiero, 2010) using panel data by means of spatial-lag and spatial error econometric approaches: the corrected 2SLS approach suggested by Beenstock and Felsenstein (2007) and the system GMM approach proposed by Kukenova and Monteiro (2009) and Bouayad-Agha and Védrine (2010). However, the results were not encouraging. This could be due to the fact that our data set is characterized by a low T and a low N.

consumption is measured by the number of defined daily doses per 1,000 inhabitants per day (DID). A defined daily dose represents the standard dose necessary for one day of drug treatment in adults and is defined by an independent scientific committee answering to the WHO Collaborating Center for Drug Statistics Methodology. The DID measure can be interpreted as the number of persons (out of 1,000) who are taking antibiotics on a given day(WHO, 1996).

The mean level of consumption of outpatient antibiotics in Italy between 2000 and 2008 was23.52DID, with a peak in 2008 (25.01) and a minimum in 2000 (22.36). Figure 2shows that antimicrobials use has been roughly stable over time but a remarkable degree of heterogeneity in consumption is observed across the regions. Generally, regions in central Italy use more antibiotics *per capita* (24.94 DID) than regions in the north (18.42 DID) and less than southern regions and the islands (27.91 DID).

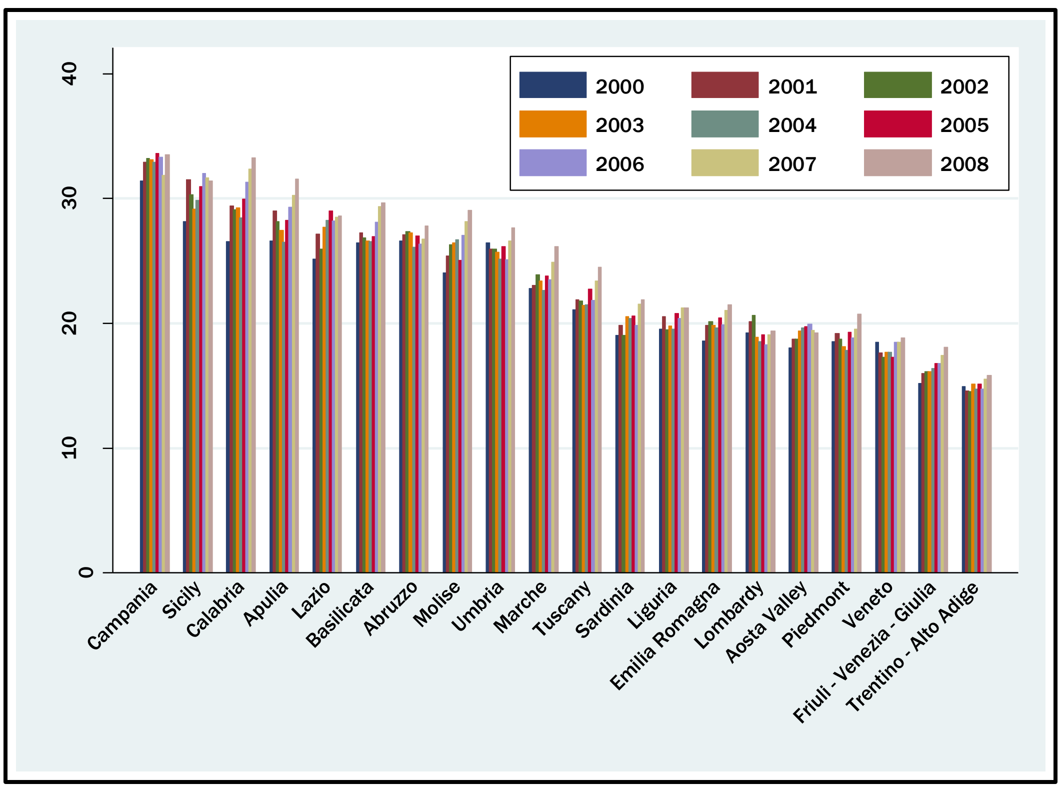

Figure 2: Outpatient antibiotic use in Italy by region and year.

Information on the demographic structure of the population and density, *per capita* income, density of general practices and rate of infectious diseases were taken from the Italian National Institute of Statistics (Istat). Copayments were obtained from annual reports on pharmaceutical consumption and expenditure prepared by Osmed.

Regional copayments vary from 0 to 4 Euros. We rescaled the variable from 1 to 5 in order to avoid negative values in the log transformation. In the LSDVC and GMM-BB estimations, we use the lagged rate of infections to tackle possible endogeneity. Finally, it has to be noted that generally the variables considered in the model show a relative low within variation. Summary statistics are reported in Table 1.

Variable	Variable description	Mean value by year *								
		2000	2001	2002	2003	2004	2005	2006	2007	2008
DID	Defined daily doses per 1,000 inhabitants	22.36	23.37	23.19	23.16	22.96	23.65	23.68	24.37	25.01
		(4.6647)	(5.2823)	(5.2066)	(5.0900)	(5.0702)	(5.2126)	(5.5173)	(5.3457)	(5.5405)
Y	Income *per capita* (in Euro)	20292	21260	21913	22394	23110	23539	24409	25246	25473
		(5203.703)	(5365.841)	(5509.915)	(5634.775)	(5817.211)	(5844.966)	(5893.223)	(6088.59)	(6150.54)
POP_1	Proportion of population aged 0-24	25.58	25.18	24.81	24.50	24.27	24.11	23.99	23.88	23.81
		(4.243)	(4.101)	(3.956)	(3.808)	(3.636)	(3.444)	(3.258)	(3.059)	(2.863)
POP_2	Proportion of population aged 25-64	55.36	55.49	55.58	55.65	55.66	55.57	55.48	55.46	55.46
		(2.357)	(2.276)	(2.189)	(2.088)	(1.961)	(1.818)	(1.649)	(1.468)	(1.309)
POP_3	Proportion of population aged above 64	19.04	19.32	19.59	19.84	20.06	20.30	20.52	20.64	20.71
		(2.920)	(2.895)	(2.877)	(2.869)	(2.837)	(2.768)	(2.702)	(2.641)	(2.559)
DPOP	Population density	174.37	174.42	174.91	176.2	177.82	179.09	180.059	181.273	182.577
		(106.173)	(106.161)	(106.450)	(107.279)	(108.426)	(109.355)	(110.159)	(111.037)	(111.776)
INF	Incidence of infections per 100,000 inhabitants	354.76	316.96	317.70	329.04	302.99	216.25	236.13	213.89	208.76
		(235.915)	(224.020)	(152.282)	(173.007)	(168.503)	(119.663)	(144.240)	(156.629)	(171.408)
DPH	Density of physicians for 1,000 inhabitants	0.8336	0.8292	0.8271	0.8271	0.8224	0.8181	0.8200	0.8220	0.8214
		(0.0624)	(0.0595)	(0.0564)	(0.0595)	(0.0601)	(0.0597)	(0.0597)	(0.0604)	(0.0600)
P	Copayment	1.50	0	0.83	0.85	0.95	0.70	0.65	0.95	1.10
		(0)	(0)	(0.92)	(0.92)	(0.94)	(0.92)	(0.93)	(1.19)	(1.18)

* Standard errors in parenthesis

Table 1: Descriptive statistics

5. Results

In this section we discuss the results obtained from the estimation of the dynamic model of antibiotic consumption defined by equation (6) above. The model is estimated by means of the GMM-BB and the corrected LSDV estimators. For comparison purposes, we also perform OLS (upper bound) and LSDV (lower bound) estimations. Findings are summarized in Table 2 and Table 3. The GMM-BB estimates are shown together with the *p*-value of the test statistics of serial correlation (AR1, AR2) and overidentifying restrictions (Sargan). The *p*-values of these statistics show that there is no significant second-order autocorrelation, which is the crucial aspect with respect to the validity of the instruments. Moreover, the *p*-value of the Sargan test statistics indicates that the null hypothesis that the overidentifying conditions are correct cannot be rejected.

	OLS Obs: 160 $R^2 = 0.9795$		**LSDV** Obs: 160 F-test = 18.24****	
Variables	**Coeff.**	**Std. Err.**	**Coeff.**	**Std. Err.**
Constant	- 0.327565	0.434188	- 2.814276 **	0.797062
P	- 0.017514 ***	0.006209	- 0.021550 ***	0.007148
Y	0.054888	0.032295	0.594555 ****	0.097423
POP_1	0.010594 ***	0.003670	- 0.002333	0.005903
POP_2	0.007859 **	0.002910	- 0.017877	0.012516
DPOP	0.000098 **	0.000036	- 0.001112	0.000866
EDU	- 0.001949	0.001331	- 0.006792 ***	0.002377
DPH	0.092545	0.097387	0.1013074	0.175096
INF	- 0.000119 ****	0.000030	- 0.000074 ***	0.000034
NORTH	- 0.048268 **	0.020042	-	-
CENTER	- 0.019377	0.016180	-	-
DID_{t-1}	0.808902 ****	0.038910	0.206029 ***	0.079935

* significant at 10%   ** significant at 5%   *** significant at 1%   **** significant at 0.1%

Table 2: OLS and LSDV estimates.

	LSDVC Obs: 140		GMM-BB Obs: 160	
Variables	**Coeff.**	**Std. Err.**	**Coeff.**	**Std. Err.**
Constant	–	–	- 1.984774	0.773706
P	- 0.024388 ***	0.007962	- 0.035092 ***	0.010869
Y	0.527978 ****	0.098532	0.323509 ****	0.080521
POP_1	0.008434	0.008766	0.006294	0.006254
POP_2	- 0.016646	0.014109	0.004361	0.011409
DPOP	- 0.000802	0.000972	0.000452 **	0.000234
DPH	0.214512	0.188081	0.331218	0.410791
INF	0.000047 *	0.000039	0.000063	0.000040
NORTH	–	–	- 0.439739 ***	0.218480
CENTER	–	–	- 0.320512 ****	0.053227
DID_{t-1}	0.383533 ****	0.095357	0.487162 ***	0.196898
Sargan test (p-value)	–	–	0.211	
Arellano-Bond (AR1) test (p-value)	–	–	0.002	
Arellano-Bond (AR2) test (p-value)	–	–	0.194	

* significant at 10% ** significant at 5% *** significant at 1% **** significant at 0.1%

Table 3: LSDVC and GMM-BB estimates for antibiotic consumption.

In both models the number of statistically significant parameter estimates is relatively low. However, the results are satisfactory as far as the coefficients of the price variables and the coefficients of the lagged variables, which are used for the estimation of the latent impact of antibiotic resistance, are significant and carry the expected sign in both models. Nevertheless, the values of these coefficients are relatively different between the two models. As expected, the largest difference concern the coefficient of the lagged dependent variable (DID_{t-1}). The LSDVC approach leads to a lower coefficient estimate of the lagged variable. Finally, the significance of the lagged variable is also of relevance because it allows for the analysis of the impact of bacterial resistance on antibiotic consumption.

Generally, the results obtained using the GMM-BB estimator show that income and the rate of infectious diseases seem to have a notable influence on antibiotic consumption. Only the coefficients of the share of the population and the density of doctors are not significant. The results show that antibiotic consumption is generally lower in central and northern Italian regions. Although the likelihood of infections transmission is expected to be higher in populated regions compared to relatively remote regions, the coefficient of population density is positive, but not significant.

The results obtained using the LSDVC estimator show that only coefficients of the price, income, and rate of infectious diseases, are significant. Regarding the significance of the coefficients, it is worth noting that several variables considered in the analysis have limited variation within regions over time. The coefficients of the explanatory variables can be "imprecise" if variation over time is dominated by variation across regions, i.e. the "between" variation (Cameron and Trivedi, 2005). Low "within" variation can explain the small number of significant coefficients.

Since weuse a hybrid log-log model specification, some coefficients can be interpreted as elasticity. The outcome advances that regions with a higher level of income, i.e. northern regions, use less antibiotics *ceteris paribus.* Similar results have been obtained using cross-sectional data by Filippini *et al.* (2009a) who focus on antibiotic consumption across small geographic areas in Switzerland and by Baye *et al.* (1997) using USA data. Hence, the result from our dynamic approach reinforces the evidence of positive income effects.

In accordance with the economic theory, we find a statistically significant and negative association between antibiotic consumption and price/copayment in both models, even though this impact is relatively low. Using a natural experiment across Italian regions, Fiorio and Siciliani (2009) investigated the effect of copayments on drug prescriptions. They found that an increase in the copayment by one Euro reduces the per capita number of prescriptions by 4% and per capita public pharmaceutical expenditures by 3.4%. They also found evidence that when in 2006 some regions reduced (but not removed) the copayment, a reduction in the copayment by one Euro increases the *per capita* number of prescriptions by 3.4%.

The dynamics of antibiotic use is captured by the coefficient of the lagged variable of consumption. In both models this coefficient is positive and statistically significant (0.383 and 0.487). This suggests that the adjustment speed is substantially fast. In fact, individuals close 61.7% (in the LSDVC estimation) and 51.3 % (in the GMM-BB estimation) of the gap between current and desired antibiotic consumption within one year. The full adjustment occurs in approximately 1.62 years if we consider the estimation results of the LSDVC; 1.94 years using the GMM-BB estimation results. In other words, antibiotic consumption seems to move towards optimal levels quite fast. We can conclude that persistence in consumption is relatively weak, which suggests that individuals set their level of antimicrobial use over time close to the optimal level.

6. Conclusions

Antibiotics misuse increases the threat of bacterial resistance which in turn reduces antibiotic effectiveness over time (Elbasha, 2003). The understanding of factors influencing the dynamics of antibiotic consumption may then contribute to the shaping of appropriate measures of public interventions to optimise the use of antimicrobials. The empirical literature is lacking in this respect.

In this paper, we propose a dynamic approach to investigate antibiotic use in outpatient care which hypothesises that antibiotic consumption is affected by antibiotic inefficacy, i.e. the stock of bacterial resistance to antimicrobials. The level of inefficacy represents a bad which is indirectly measurable by means of past antibiotic use. This represents the main novelty of our analysis and provides a significant contribution to the existing empirical literature on antibiotic consumption.

To some extent, antibiotics exhibit aspects which are similar to those of addictive goods, such as cigarettes. Past antibiotic use decreases the marginal benefit from consumption over time, which implies that higher levels of consumption are required to maintain the same level of treatment efficacy to cure bacterial infections. Thus, consumers adjust their current levels of consumption towards optimal levels depending of the expected benefits from antibiotic treatment and the costs of bacterial resistance.

We show that individuals adjust their levels of consumption in a relatively short period. Hence, outpatient antibiotic consumption exhibits a low degree of persistence. The rationale may be that bacterial resistance represents a constraint which can hardly be ignored by consumers unless incurring in dangerous threats to their health.

Our findings may also suggest that public policies to preserve antibiotic efficacy could be improved. Efforts to restrict antibiotic use in outpatients have been much less successful than in hospitals because no central agent (such as a hospital administrator or infection control committee) can enforce an antibiotic policy (Harbarth and Samore, 2005). Moreover, the high costs of malpractice lawsuits may induce doctors to use stronger and broader spectrum antibiotics more frequently than it would be necessary. This tendency may increase the level of resistance in the community, but the impact of each individual treatment is so small that doctor's perceived benefit from antibiotic prescriptions often outweighs the small uncertain costs associated with increased resistance (Brown and Layton, 1996). Finally, it has been asserted that policies on patent protection for antimicrobial drugs may not be optimal. Allowing for longer patent life could increase incentives for pharmaceutical firms to minimise resistance, since companies would enjoy a longer period of monopoly benefits from their antibiotic effectiveness (Herrmann, 2010).

Further research is desirable to assess the impact of public policies in preserving antibiotic effectiveness.

References

Anderson TW and Hsiao Ch (1982) Formulation and Estimation of Dynamic Models Using Panel Data. *Journal of Econometrics* 18: 47-82

Arellano M and Bond S (1991) Some tests of specification for panel data: Monte Carlo evidence and an application to employment equations. *Review of Economic Studies* 58, 277-297

Baltagi B and Levin D (1986) Estimating dynamic demand for cigarettes using panel data: the effects of bootlegging, taxation, and advertising reconsidered. *Review of Economics and Statistics* 68(1): 148-156

Baltagi B (2002) Econometric analysis of panel data. John Wiley & Sons, USA

Baye MR *et al.* (1997) Demand systems and the true sub-index of the cost of living for pharmaceuticals. *Applied Economics* 29: 1179–1189.

Becker G and Murphy K (1988) A theory of rational addiction. *The Journal of Political Economy* 96: 675-700

Becker G *et al.* (1991) Rational addiction and the effect of price on consumption. *American Economic Review* 81(2): 237-241

Becker G *et al.* (1994) An empirical analysis of cigarette addiction. *American Economic Review* 84(3): 396-418.

Beenstock M and Felsenstein D (2007) Spatial vector autoregressions. *Spatial Economic Analysis* 2(2): 167-196

Blundell RW and Bond S (1998) Initial Conditions and Moment Restrictions in Dynamic Panel Data Models. *Journal of Econometrics* 87, 115-143.

Bouayad-Agha S and Védrine L (2010) Estimation strategies for spatial dynamic panel using GMM. A new approach to the convergence issue of European regions. *Spatial Economic Analysis* 5(2): 205-227.

Boyer M (1983) Rational demand and expenditure patterns under habit formation. *Journal of Economic Theory* 31: 27-53

Bretteville-Jensen AL (2006) Drug demand – initiation, continuation and quitting – *De Economist* 154: 491-516

Brown G and Layton D (1996) Resistance economics: social cost and the evolution of antibiotic resistance. *Environmental and Development Economics* 1: 349-355

Cameron A and Trivedi P (2005) Microeconometrics. Methods and Applications. Cambridge University Press, Cambridge

Chaloupka F (1991) Rational addiction and cigarette smoking. *The Journal of Political Economy* 99(4): 722-742

Cizman M (2003) The use and resistance to antibiotics in the community. *International Journal of Antimicrobial Agents* 21: 297-307

Coast J *et al.* (1998) An economic perspective on policy to reduce antimicrobial resistance. *Social Science & Medicine* 46(1): 29-38.

Elbasha E (2003) Deadweight loss of bacterial resistance due to overtreatment. *Health Economics* 12: 125-138.

Filippini M *et al.* (2006) Socioeconomic determinants of regional differences in outpatient consumption: Evidence from Switzerland. *Health Policy* 78: 77-92.

Filippini M *et al.* (2009a) Small area variations and welfare loss in the use of outpatient antibiotics. *Health Economics, Policy and Low* 4: 55-77.

Filippini M *et al.* (2009b) Regional consumption of antibiotics: A demand system approach. *Economic Modelling* 26:1389-1397

Fiorio C and Siciliani L (2010) Co-payments and the demand for pharmaceuticals: Evidence from Italy. *Economic Modelling* 27(4):835-841

González L and Masiero G (2010) Antibiotic consumption in Italy: a spatial panel approach. USI Working paper forthcoming.

Gorman WM (1967) Tastes habits and choices. *International Economic Review* 8(2): 218-222

Harbarth S and Samore M (2005) Antimicrobial resistance. Determinants and future control. *Emerging Infectious Diseases* 11(6): 794-801

Herrmann M and Gaudet G (2009) The economic dynamics of antibiotic efficacy under open access. *Journal of Environmental Economics and Management* 57: 334-350

Herrmann M (2010) Monopoly pricing of an antibiotic subject to bacterial resistance. *Journal of Health Economics* 29(1): 137-150

Huttner B, Goossens H, Verheij T, Harbarth S, on behalf of the CHAMP consortium (2010) Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *The Lancet Infectious Diseases* 10:17–31

Johnson J and Oskanen EH (1977) Estimation of demand for alcoholic beverages in Canada from pooled time series and cross sections. *Review of Economics and Statistics* 59(1): 113-118

Judson R and Owen A (1999) Estimating dynamic panel data models: a guide for macroeconomist. *Economics Letters* 65:9-15.

Kern W *et al.* (2006) Regional variation in outpatient antibiotic prescribing in Germany. *Infection* 34(5): 269-273

Kiviet JF (1995) On bias, inconsistency and efficiency of various estimators in dynamic panel data models. *Journal of Econometrics* 68: 53-78

Kukenova M and Monteiro JA (2009) Spatial dynamic panel model and system GMM: A Monte Carlo investigation, Munich Personnal RePEc Archive Paper No.11569

Laxminarayan R (2001) Fighting antibiotic resistance: Can economic incentives play a role? *Resources* 143: 9-12

Laxminarayan R and Brown G (2001) Economics of antibiotic resistance: a theory of optimal use. *Journal of Environmental Economics and Management* 42(2): 183-206

Laxminarayan R and Weitzman ML (2002) On the Implications of Endogenous Resistance to Medications. *Journal of Health Economics* 21(4): 709–18

Lindquist J (2010)*et al.* Effective degree network diseases models. *Journal of Mathematical Biology* 62: 143-164

Luo *et al.* (2003) Cigarette smoking in Japan: examination of myopic and rational models of addictive behavior. *Journal of Family and Economic Issues* 24(3): 305-317

Masiero G *et al.* (2010) Socioeconomic determinants of outpatient antibiotic use in Europe. *International Journal of Public Health* 55: 469-478

Matuz M *et al.* (2005) Regional variations in community consumption of antibiotics in Hungary, 1996-2003. *British Journal of Clinical Pharmacology* 61(1): 96-100

Mera RM *et al.* (2006) Antibacterial use and *Streptococcus pneumoniae* penicillin resistance: a temporal relationship model. *Microbial Drug Resistance* 12(3): 158-163

Monroe S and Polk R (2000) Antimicrobial use and bacterial resistance. *Current Opinion in Microbiology* 3: 496-501

Nitzan O *et al.* (2010) Variability in outpatient antimicrobial consumption in Israel. *Infection* 38(1): 12-18

Nordberg P *et al.* (2005) Consumers and providers – Could they make better use of antibiotics? *International Journal of Risk & Safety in Medicine* 17:117-125

Peper A (2004) A theory of drug tolerance and dependence I: a conceptual analysis. *Journal of Theoretical Biology* 229: 477-490.

Pollak RA (1970) Habit formation and dynamic demand functions, *Journal of Political Economy* 78: 748-763.

Pollak RA (1976) Habit formation and long-run utility functions. *Journal of Economic Theory* 13: 272-297

Rudholm N (2002) Economic implications of antibiotic resistance in a global economy. *Journal of Health Economics* 21: 1071-1083

Sachs L and Tomson G(1992) Medicines and culture –a double perspective on drug utilization in a developing country –*Social Science and Medicine* 34: 307-315

Spinnewyn F (1981) Rational habit formation. *European Economic Review* 15: 91-109

Stigler G and Becker G(1977) *De gustibus non est disputandum. American Economic Review* 67(2): 76-90

Tiezzi S (2005) An empirical analysis of tobacco addiction in Italy. *The European Journal of Health Economics* 6(3):233-243

Wilen JE, Msangi S (2003) Dynamics of antibiotic use: ecological versus interventionist strategies to manage resistance to antibiotics. In: Laxminarayan R (Ed), Battling resistance to antibiotics and pesticides: An economic approach. Washington, DC 17-41

WHO Collaborating Centre for Drug Statistics Methodology (1996). Guidelines for ATC Classification and DDD Assignment. Oslo, Norway

Assessing the impact of policies towards the efficient use of antibiotics

1. Introduction

The overuse of antibiotics is the main force driving the increase of bacterial resistance, which represents a major threat to public health. Indeed, since antimicrobials are frequently prescribed for viral infections and are widely available over-the-counter in many countries, medication may lose effectiveness (Llor and Cots, 2009). Large volumes of antimicrobials are also used in agriculture and veterinary medicine, and in many consumer products where benefits are often dubious (Tan *et al.*, 2002).

Efforts to reduce bacterial resistance through a control of antibiotic use have focused on surveillance, reducing prescribing rates, and limiting the use of antibiotics in agriculture and food-producing animals. More recently, attention turned to promoting appropriate and safe consumption of antibiotics in the community (Sabuncu *et al.* 2009). Because the association between antibiotic use and bacterial resistance may cross regional borders within countries, the implementation of national policies has emerged as an important tool for controlling and reversing bacterial resistance. Nevertheless, the effects of these policies are still unclear.

The aim of this study is to assess the impact of public education campaigns on antibiotic use in Europe. Using information on national campaigns provided by the public health literature and data on antibiotic use and socioeconomic determinants for an 11-years period (1997-2007), we apply a differences-in-differences econometric approach. We control for unobserved individual heterogeneity by means of fixed-effects estimations and address endogeneity aspects of infections and policies with lagged and instrumental variables methods.

Many studies describe and review national policies towards antibiotic consumption. However, the literature lacks of studies on the impact of policies. Recently, Huttner *et al.* (2010) described the characteristics of public campaigns in high-income countries but failed to provide statistical evidence on their impact on antibiotic use. Other studies focused on specific countries. For instance, Goossen *et al.* (2006) compared policies towards the efficient use of antibiotics in Belgium and France. Socioeconomic determinants of antibiotic use across Europe have been recently investigated by Masiero *et al.* (2010) using random-effects regressions. The effect of public policies towards the consumption of antimicrobials is neglected.

The remaining of the paper is organized as follows. In Section 2 we summarize the literature on policies towards the use of antibiotics, and provide a brief overview of public interventions implemented in European countries. In Section 3 we propose an econometric model of antibiotic consumption where the impact of national campaigns is assessed after controlling for the main determinants of consumption. Data are described in Section 4. Estimation results and discussion of main findings are presented in Section 5. Section 6 concludes.

2. Public policies towards antibiotic consumption

From the economic point of view, antimicrobial agents are a scarce resource since antibiotics effectiveness decreases because of bacterial resistance. Public policies represent an important way to tackle the problem. We shortly characterize them by looking at the type of intervention, the geographical area involved, targeted agents, the instruments used an their main message.

Policies to improve the use of antibiotics can be classified as educational, managerial, regulatory, and economic (Quick *et al.*, 1991). Educational interventions are persuasive in nature and include training of prescribers via face to face visits, seminars, workshops, supervisory visits and various printed materials aimed at patients or prescribers. Managerial strategies aim at guiding decision-making. They may focus on the selection and procurement, performing drug utilization reviews, providing cost information, prescribing with standard treatment guidelines, and packaging full courses of therapy. Regulatory interventions constraint prescribers by law to restrict their decision making through interventions such as registering drugs for marketing, licensing prescribers, and limiting prescribing or dispensing. Finally, economic interventions aim at providing financial incentives to institutions, providers and patients. These strategies depend on the pricing structure, the price setting and the reimbursement mechanism.

Among educational strategies to promote the appropriate use of antibiotics and to raise the public awareness of bacterial resistance, public campaigns are one of the most widely used. In Europe, the decision to launch these campaigns is generally taken by the health authorities.

Policies can be implemented at national or subnational level, although public campaigns for a more rational use of antibiotics are generally implemented as part of a national strategy to reduce resistance to antimicrobials (Huttner *et al.*, 2010). There is also a tendency to involve international organizations. Rudholm (2002) suggests that the problem of resistance is a global one. Consequently, optimal policies should consider the fact that antibiotic resistance can cross country borders and travel far distances. Coast *et al.* (1998) argue that policies aimed at reducing antibiotic use within a country may not work in another country since local epidemiological factors affect the spreading mechanism of antibiotic resistance.

The majority of public campaigns are addressed to the general public, focusing on parents of young children. Health-care professionals, specifically primary care physicians, are also targeted. The public is targeted by distributing informational material to patients and by displaying posters in waiting rooms and pharmacies. General practitioners receive educational material such as guidelines, information sheets and booklets. Some campaigns use several mass media such as television, radio, printed material, billboards, and public-transport advertisement. The use of the internet to spread information about the program is common to almost all campaigns.

Most campaigns attempt to educate the public that antibiotics are not needed for treating viral infections. They focus on respiratory tract infections and use a mix of negative and positive messages. The main message is that bacterial resistance is a major public health issue largely caused by the misuse of antibiotics. Hence, it encourages people to follow rigorously the antibiotic dosage regime prescribed by the physician.

2.1 Empirical studies on the impact of policies

The literature on the impact of antibiotic policies is limited to descriptive studies. Goosens *et al.* (2006) analyse national campaigns in two European countries with high antibiotic use, Belgium and France, between 1997 and 2003. To assess the impact of antibiotic policies, the authors compare rates of antibiotic consumption between the two countries and England, where rates of antibiotic use are lower and persistent. The study concludes that carefully designed mass education campaigns could be effective in reducing antibiotic use at national level. The authors do not use statistical approaches to control for differences between countries related to the impact of infections, the characteristics of prescribers or demographic aspects, over the time period considered.

To assess the impact of antibiotic policies in Central and Easter European (CEE) countries, Cizman *et al.* (2004) apply a questionnaire to national representatives. The questionnaire includes information about national antimicrobial resistance surveillance, national consumption of antibiotics in the community and in hospitals, and strategies to optimize the use of antimicrobials. The authors then list countries which have restricted the use of some antibiotics for out-patients and in-patients and briefly describe other types of interventions implemented. Findings show that only few countries have restricted the use of antimicrobials in ambulatory care as compared to the common practice of restricting the use of antibiotics in hospitals. The impact of antibiotic policies is not assessed.

Using a comprehensive search strategy and structured interviews, Huttner *et al.* (2010) identify and review the characteristics and outcomes of 22 public campaigns for a more rational use of antibiotics done at a national or regional level in high-income countries between 1990 and 2007. The majority of these campaigns (16) were located in Europe. Looking at data on the consumption of outpatient antibiotics, the authors try to evaluate the effect of the campaigns. Most campaigns do not have a control population and trends in consumption before the interventions are not considered. The analysis cannot disentangle whether antibiotic consumption would still have increased without the campaign or if the duration of the intervention was too short to observe measurable effects. The study can only suggest a relationship between a reduction in the use of antibiotics and the implementation of a public campaign since powerful statistical tools are lacking.

In conclusion, evidence suggested by current empirical studies on the impact of antibiotic policies is based on descriptive statistics and graphical analysis. An econometric approach could then provide more convincing evidence on the association between the adoption of campaigns and antibiotic consumption rates.

3. The empirical specification

To investigate the effects of national campaigns for a more rational use of antibiotics, we estimate an econometric model of outpatients antibiotic consumption using a panel dataset for a sample of European countries.

Our model serves as a reduced form that considered both demand and supply factors. In our simple frame, individuals are assumed to follow doctors' prescriptions and to be compliant with the antibiotic therapy. In the empirical specification of the model, the consumption of outpatient antibiotics is assumed to depend upon socio-demographic characteristics of the population, individuals' health status, antibiotic price, the characteristics of health care supply and information on national campaigns for a more rational consumption of antibiotics.

Our data set includes countries that implemented a policy intervention to reduce antibiotic consumption, as well countries that did not adopt any type of campaign. Moreover, we have information on antibiotic consumption before and after a policy has been introduced. This aspect of the panel allows to estimate the effect of policy interventions using a difference-in-differences (diff-in-diff) approach (Bertrand *et al.*, 2004). The general idea of this approach is to compare the outcome, in this case the *per capita* consumption of antibiotics, of two groups of countries before and after the introduction of a campaign to reduce antibiotic consumption. One group, denoted the “control”, is composed of countries that did not introduce any policy instrument to reduce antibiotic consumption. The other group, the “treatment”, includes all countries that have adopted some policy. Looking at differences in outcomes between the two groups observed after the introduction of a policy we can estimate the impact of policy interventions. The typical diff-in-diff estimation with panel data with more than two periods considers countries and years fixed effects. Therefore, the diff-in-diff estimation takes into account unobserved time-invariant variables.

Our empirical approach draws from Giavazzi and Tabellini (2005) who apply a difference-in-difference approach to investigate the impact of economic and political liberalizations on economic performance, macroeconomic policy and structural policies. We estimate the following model on the whole sample of treated and control countries:

$$DID_{it} = \beta_0 + \beta_1 POLICY_{it} + \beta' x_{it} + \omega_i + v_t + \varepsilon_{it}, \tag{1}$$

where DID_{it} denotes defined daily doses of antibiotic consumption per 1,000 inhabitants in country *i* at time *t*. $POLICY_{it}$ is a dummy variable which assumes a value equal to 1 in the year of policy implementation and in the following years, and 0 otherwise. As already discussed, a typical policy instrument used by the government is to organize an information campaign for a rational use of antibiotics. x_{it} is a set of covariates which includes the *per capita* national income (Y_{it}), the physicians' density (DPH_{it}), the percentage of the population below 14 years of age, between 15 and 24, 25 and 64, 65 and 79, and over 80 ($POP_{1it} \dots POP_{5it}$), the price level for a defined daily dose of antibiotics (P_{it}), and the population health status measured by the impact of infections (INF_{it}). ω_i captures the country-level fixed effects, which are assumed constant over time; and v_t is the year-specific fixed effect, which is assumed constant across countries. Finally, ε_{it} is an unobserved error term with Z distribution.

By including both time and country fixed effects, we are able to distinguish the impact of campaigns *per se* from other determinants having to do with country characteristics or time effects. The main coefficient of interest is β_1 which measures the effect of the campaigns on antibiotic consumption.

In order to identify the impact of policy interventions some assumptions have to be satisfied. First, we have to exclude the presence of unobserved variables affecting antibiotic consumption that moves systematically over time in a different way between the two groups of countries. In this study the assumption sounds reasonable because all countries belong to Europe and, therefore, the general trends should be relatively similar. Further, we have to assume that policies are exogenous, e.g. the decision to introduce a public campaign is independent on the level of antibiotics consumption in a country. This assumption is also reasonable because the pressure to promote information campaigns does not directly depend on antibiotic consumption. It probably depends on increasing levels of antibiotic resistance. Clearly, antibiotic resistance is also indirectly caused by the consumption of antibiotics.

Potential endogeneity problems may lead to biased results in the estimation of Equation (1). In our case two explanatory variables are potentially endogenous: infections and policies. Infections are potentially endogenous since a low level of antibiotic use may favour poorer health conditions in the population, i.e. an increased incidence of infections. To tackle this problem, we estimate two models. In Model 1, following Masiero *et al.* (2010), we use the lagged mortality rate for infectious diseases (INF_{it-1} instead of INF_{it}). This is a simple instrumental variable approach though pretty efficacious.

As for public campaigns, these may be driven by high levels of antibiotic use in a country. In order to check the robustness of the results of Model 1, we endogeneize the policy variable using an instrumental variable approach (Model 2). Unfortunately, as we will explain later, the limited number of instruments, reduces the number of observations. The population density, women employment rate, the production of milk and pigs, the use of fertilizers, and the size of the country are used as instruments for policies. These variables should indirectly measure the level of bacterial resistance within a country (Masiero *et al*., 2010). In contrast to bacterial resistance, they are poorly correlated with antibiotic use. Consequently, they can reasonably be used as instruments for policies.

Finally, diff-in-diff estimation results can be affected by positive serial correlation (see Bertrand *et al*., 2004). To cope with this problem, we report standards errors clustered by country.

4. Data

The consumption rate of antibiotics is most commonly expressed as the number of defined daily doses (DDDs) per 1,000 inhabitants per day. The DDD is a technical unit based on the assumed average maintenance dose per day for a drug used for its main indication in adults. Antibiotic use is standardized using the ATC/DDD index for international drug consumption studies (WHO, 2011).

Antibiotic prescribing practices vary widely across countries. Mean figures of defined daily doses per 1,000 inhabitants for 21 European countries collected by the European Surveillance of Antimicrobial Consumption (ESAC) project between 1997 and 2007 show that France, Greece, and Luxembourg, among others, exhibit significantly higher values of antibiotic use than Austria, Denmark, and the Netherlands (see Figure 1).[19] The

[19] Data are reliable and exhibit a good degree of comparability since the ESAC network screened for detection bias in sample and census data, bias by over-the counter sales and parallel trade, errors in assigning medicinal product packages to the Anatomical Therapeutic Chemical Classification (ATC), and errors in calculations of defined daily doses (Vander Stichele *et al*., 2004).

magnitude of these differences partially mirror differences in the levels of bacterial resistance (Figure 2), collected by the European Antimicrobial Resistance Surveillance System (EARSS) and measured by the rate of penicillin-non-susceptible *Streptoccoccus pneumonia* isolates (PNSP).

Annual data available on determinants of outpatient antibiotic use between 1997 and 2007 are summarised in Table 1. These include socioeconomic characteristics of the population (income and demographic structure), supply-side factors (density of doctors), price of antibiotics, and the incidence of infections measured by the mortality rate. We use the mortality rate for infectious diseases as a proxy for the incidence of infections since morbidity indicators are less complete and reliable.

Data were obtained from a variety of sources. Information on *per capit*a income (measured in US dollars in purchasing power parity), density of physicians, and the incidence of infections were extracted from publications by the OECD (2010). The demographic structure of the population was derived from Eurostat tables (Eurostat, 2010).

I derived price levels for antibiotics by combining information from two indicators: the comparative price level index (PLI) and the harmonized annual average price index (HICP) for pharmaceutical products. The PLI indicates the price level of each country compared to the average price level of the 25 EU countries in 2005. The HICP includes information on price trends for pharmaceuticals for each country during 2000 and 2005, where 2005=100. These indices are provided by Eurostat.

As for public campaigns data collection is cumbersome and may result in incomplete data. Also little information is available in scientific journals. For our purpose, we draw information on campaign characteristics from the recent review by Huttner *et al.* (2010). The authors identify public campaigns implemented at national level in high income countries

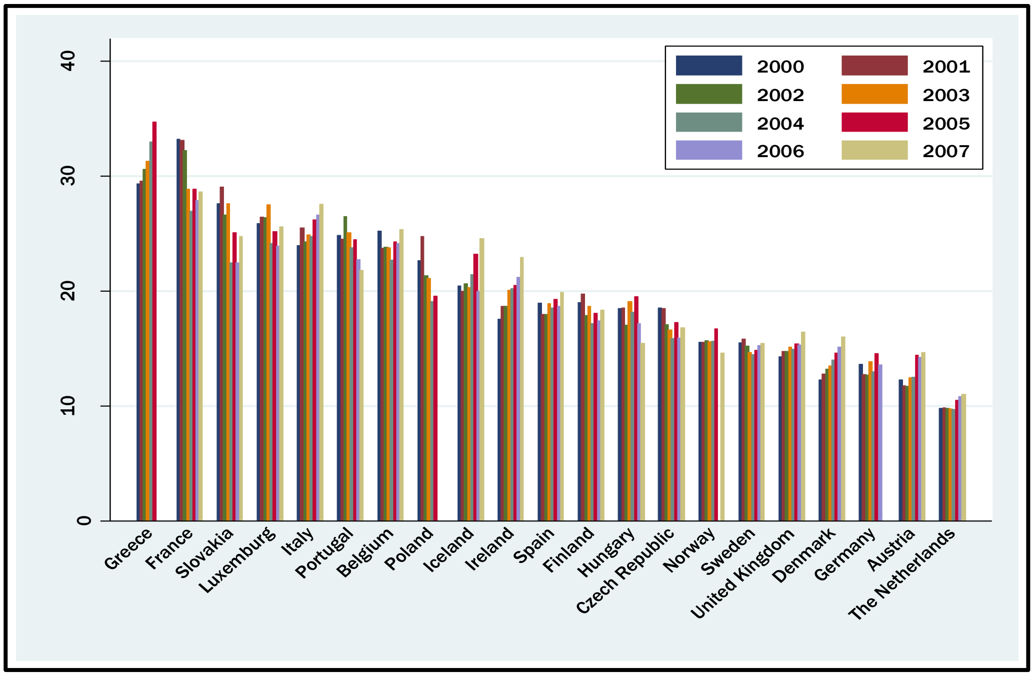

Figure 1: Outpatient antibiotic use in Europe by country and year [in DID = defined daily doses (DDD) per 1,000 inhabitants per day]. Data source: European Surveillance of Antimicrobial Consumption (2007).

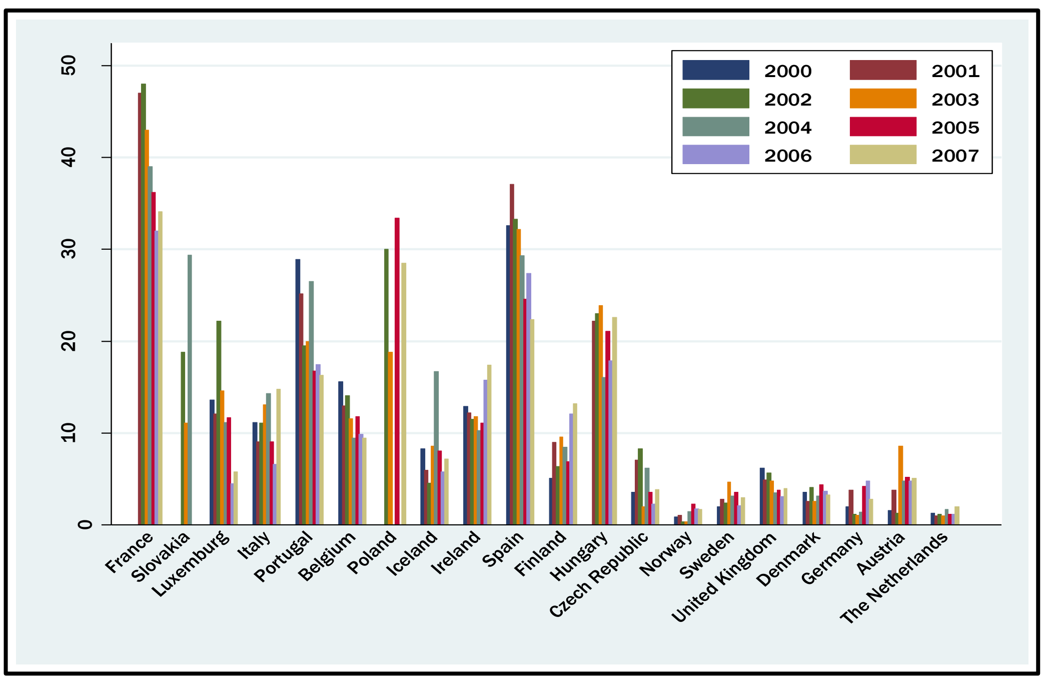

Figure 2: Levels of bacterial resistance by country and year [in PNSP = rate of penicillin-non-susceptible *Streptococcus pneumonia* isolates]. Data source: European Antimicrobial Resistance Surveillance System (EARSS).

Variable	Variable description	Mean	Std. dev.	Minimum	Maximum
Outpatient antibiotic consumption	DDDs per 1,000 inhab. per day (*DID*)	19.87	5.83	9.75	34.73
Income per capita	GDP in PPP / population (*Y*)	26'802.27	10'363.57	8'898.00	71'400.00
Antibiotic price	Comparative price levels for pharmaceutical products (*P*)	95.23	23.81	36.65	165.58
Demographic structure of population	Population under 14 / population (POP_1)	17.78	2.36	13.90	25.70
	Population 15-24 / population (POP_2)	13.29	1.83	10.20	17.50
	Population 25-64 / population (POP_3)	53.84	1.94	47.90	58.10
	Population 65-79 / population (POP_4)	11.55	1.55	8.20	15.20
	Population over 80 / population (POP_5)	3.54	0.82	1.80	5.40
Density of doctors	Practices / 1,000 inhabitants (*DPH*)	3.15	0.61	1.90	4.90
Bacterial resistance	Number of *PNSP* isolates / tested isolates (*RES*)	11.03	10.62	0	48.00
Infections	Mortality rate for infectious diseases (*INF*)	6.77	3.42	2.00	20.10
Population density	Population / km^2	101.93	53.92	2.91	393.90
Country area	Km^2	203'068	170'053	2'586	551'500
Animal production	Tons of cow's milk / 1,000	6'300.63	7'265.99	112.95	28'723.91
	Number of pigs / 1,000	10'509.78	15'469.91	73.72	81'321.00
Use of fertilizers	Tons / 1,000	919'186	1'115'849	15'852	4'988'800

DDD defined daily doses, *DID* defined daily doses per 1,000 inhabitants per day, *GDP* gross domestic product, *PPP* purchasing power parity, *PNSP* penicillin non-susceptible Streptococcus pneumoniae

Table 1. Variables notation and summary statistics.
Data sources: ESAC, EARSS, OECD and Eurostat.

between 1990 and 2007. Using information from this study, we generate a dummy variable ($POLICY_1$) which takes a value equal to 1 in the year of implementation of the campaign and 0 in the pre-campaign and post-campaign years (see Table 2). Alternatively, we consider a different policy indicator (*POLICY₂*). This is a dummy variable which takes the value 1 in the years of campaign adoption and in the years post-campaign, and 0 in the years before the campaign is adopted. It is worth noticing that the construction of these dummy variables was possible because the campaigns have rather similar characteristics.

Country	Year										
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Austria											
Belgium											
Czech Republic											
Germany											
Denmark											
Spain											
Finland											
Hungary											
Ireland											
Iceland											
Italy											
Luxemburg											
The Netherlands											
Poland											
Portugal											
Sweden											
Slovakia											
United Kingdom											
France											
Greece											
Norway											

Table 2. The implementation of national campaigns in Europe between 1997 and 2007 [years of campaign implementation are highlighted].

Information on instruments for policies (population density, size of the country, women employment rate, production of milk and meat of pigs, the use of fertilizers) are obtained from Eurostat statistics (Eurostat, 2010).

Since almost all countries implemented campaigns to increase public awareness of antibiotic use from 2000, and in order to get a satisfactory control group, we discard Iceland from the final dataset. Iceland adopted a campaign at the beginning of the period considered (1997 and 1998). The final dataset is an unbalanced panel dataset with 153 observations for Model 1 and 122 observations for Model 2. Since information on instrumental variables for policies is not available for all countries or years, the number of observations in Model 2 is reduced. Estimations are performed by means of the statistical software STATA (version 11.1).

5. Results

The parameter estimates from the estimation of Model 1 and Model 2 are summarised in Table 3. Most of the results reported in the table are satisfactory. It is worth noting that the key policy coefficient is significant in both models. In Model 2 the number of significant coefficients is higher than in Model 1.

The relatively low number of statistically significant coefficients of socioeconomic variables could be explained, as suggested by Cameron and Trivedi (2005), by the low within variation of these variables.

The only coefficient that deserves some comments is the one of physicians density, which is positive and significant in Model 2. This result might put forward some evidence of supply-induced demand. Though, assuming a positive relationship between the amount of prescriptions and the number of doctors *per capita* is not straightforward. It is known that countries with a greater number of doctors per inhabitant use more antibiotics than do countries with a smaller number of doctors per inhabitant (Molstad *et al.*, 2002; Masiero *et al.*, 2010), and that doctors who spend more time with their patients prescribe fewer antibiotics (Bjerrum *et al.*, 1999).

Both patients and doctors have an incentive to overuse antibiotics, but patients, who frequently view antibiotics as alternatives to aspirin and drugs for the common cold or flu, are likely to prefer antimicrobials even more than doctors. Physicians learn about drug resistance in medical school and are ethically constrained to avoid unnecessary antibiotic use. Patients, on the other hand, face an information disadvantage relative to physicians.

Since many patients expect to receive prompt treatment, the physician must decide between providing the drugs or justifying the delay to the patient. Thus, physicians overprescribe antimicrobials either to meet patient's expectations, instead of taking their time to explain to them why an antibiotic is not needed or for fear of misdiagnosing bacterial infections (Cizman, 2003).

In line with our expectations, the results obtained from the two models show that the dummy variable capturing the effect of public campaigns ($POLICY_1$) is significant and shows a negative sign.[20, 21] This result suggests that the implementation of public campaign leads to a reduction in the use of antibiotics. One could speculate that educated individuals are more likely to use antibiotics carefully since they are more informed about their implications.

Using the estimated coefficients of $POLICY_1$ in Model 1 and Model 2, we estimate that the implementation of a public campaign can reduce antibiotic consumption by 1.4 to 3.7 defined daily doses per 1,000 inhabitants. This roughly represents an impact

[20] Although not reported in the paper, we also estimate the models using the dummy variable $POLICY_2$. The results obtained from these estimations are consistent with those presented here.

[21] Random effects models, not shown here, were also estimated. The main results are not significantly affected.

between 7.2% and 18.5% on the mean level of antibiotic use in Europe between 1997 and 2007.

	Model 1		Model 2	
	Fixed-effects		Fixed-effects 2SLS	
	Obs. 153		Obs. 122	
	R^2 (overall) 0.1003		Wald χ^2 (16) = 31027.00 ****	
			R^2 (overall) 0.1548	
Variable	Coeff.	Std. Err.	Coeff.	Std. Err.
Constant	13.387730	10.815210	- 12.306560	15.418510
Y	0.000022	0.000064	0.000121	0.000118
INF_{t-1}	- 0.024336	0.131526	0.071601	0.143798
DPH	2.578951	1.729093	3.128074 ***	1.356139
POP_1	- 0.162891	0.307134	0.211355	0.458740
POP_2	- 0.507960	0.327056	- 0.076476	0.317847
POP_4	1.804238 ****	0.355211	2.198311 ****	0.480476
POP_5	- 2.185347	1.738170	- 1.936096	1.650253
P	- 0.051553	0.035080	- 0.028272	0.043339
$POLICY_1$	- 1.437221 ***	0.567455	- 3.682141 ***	1.502993
dt_2	- 0.477216	1.849433	0.280477	1.753773
dt_3	- 1.145775	1.768012	- 0.163466	1.607206
dt_4	- 1.423682	1.604730	- 0.443355	1.413800
dt_5	- 0.928832	1.452470	0.211678	1.181271
dt_6	- 1.399952	1.214497	- 0.157245	0.934440
dt_7	- 1.124569	0.919446	0.039486	0.724094
dt_8	- 1.764281 ***	0.748659	- 0.646103	0.553530
dt_9	- 0.783782	0.632412		
dt_{10}	- 1.305654 ***	0.478819		
σ_u	5.893451		5.878604	
σ_e	1.139025		1.234113	
ρ	0.963991		0.957788	

Notes: POP_3 and dt_1 are excluded from the estimations in order to avoid exact collinearity.
Standard errors are clustered by country.
σ_u standard deviation of common residuals, σ_e standard deviation of unique (individual) residuals, ρ variance not explained by differences across entities.

* significant at 10%. ** significant at 5%. *** significant at 1%. **** significant at 0.1%.

Table 3. Parameter estimates for difference-in differences models of antibiotic consumption in Europe.

6. Conclusion

Several studies have shown that a decrease in the use of antibiotics may reduce levels of bacterial resistance. During the last decade, many European countries have undertaken public health programs to optimize antibiotic use in the community (Sabuncu *et al.*, 2009). Nevertheless, the effectiveness of policies for a rationale use of antibiotics is still unclear. In particular, the influence of public campaigns on antimicrobial usage, and therefore on bacterial resistance, has not been assessed accurately (Huttner *et al.*, 2010).

In this paper, we estimated the impact of antibiotic policies in Europe by means of a difference-in-difference methodology. The approach allowed us to identify the effect of campaigns on antibiotic use by relating differential changes in antibiotic use across countries and over time to changes in the relevant policy variables. The key identification assumption in our analysis is that national policies are likely to affect antibiotic consumption more in countries where levels of bacterial resistance are higher as compared to other countries.

The results provide some evidence that the use of public campaigns represents an effective strategy to reduce the use of outpatient antibiotics. Further research is necessary to assess the impact of policy interventions on the levels of bacterial resistance through the reduction of antibiotic consumption.

References

Bennett D, Lauderdale TL, Hung CL (2009) Competing doctors, antibiotic use, and antibiotic resistance in Taiwan. Working Paper.

Bertrand M, Duflo E, and Mullainathan S (2004) How much should we trust differences-in-differences estimates? *The Quarterly Journal of Economics* 249-275

Bjerrum L, Sogaard J, Hallas J. Kragstrup J (1999) Polypharmacy in general practice: differences between practitioners. *British Journal of General Practice* 49:1 95-98

Bronzwaer SL, Cars O, Bücholz U, *et al.* (2000) A European study on the relationship between antimicrobial use and antimicrobial resistance. *Emerging Infectious Diseases* 3: 278-282

Cameron AC, Trivedi PK (2005) Microeconometrics. Cambridge University Press, New York

Cizman M (2003) The use and resistance to antibiotics in the community. *International Journal of Antimicrobial Agents* 21: 297-307

Cizman M *et al.* (2004) Antibiotic policies in Central Eastern Europe. *International Journal of Antimicrobial Agents* 24(3): 199-204

Coast J, Smith R, Millar M (1998) An economic perspective on policy to reduce antimicrobial resistance. *Social Science and Medicine* 46: 29-38

Eurostat (2010) Eurostat Statistics. http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database. Accessed April 2011

Filippini M, Masiero G, Moschetti K (2006) Socioeconomic determinants of regional differences in outpatient antibiotic consumption: Evidence from Switzerland. *Health Policy* 78:77–92

Filippini M, Masiero G, Moschetti K (2009a) Small area variations and welfare loss in the use of outpatient antibiotics. *Health Economics, Policy and Law* 4:55–77

Filippini M, Masiero G,Moschetti K (2009b) Regional consumption of antibiotics: a demand system approach. *Economic Modelling* 26:1389–1397

Giavazzi F, Tabellini G (2005) Economic and political liberalizations. *Journal of Monetary Economics* 52: 1297-1330

Goossens H, Sprenger M (1998) Community acquired infection and bacterial resistance. *British Medical Journal* 7159: 654-656

Goossens H, *et al.* (2006) National campaigns to improve antibiotic use. *European Journal of Clinical Pharmacology* 62: 373-379

Huttner B, Goossens H, Verheij T, Harbarth S, on behalf of the CHAMP consortium (2010) Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *The Lancet Infectious Diseases* 10:17–31

Llor C and Cots JM (2009) The sale of antibiotics without prescription in pharmacies in Catalonia, Spain. *Clinical Infectious Diseases* 48: 1345-9

Masiero G, Filippini M, Ferech M, Goossens H (2010) Socioeconomic determinants of outpatient antibiotic use in Europe. *International Journal of Public Health* 55:469-478

Molstad S, Lundborg CS, Karlsson AK, Cars O (2002) Antibiotic prescription rates vary markedly between 13 European countries. *Scandinavian Journal of Infectious Diseases* 34: 366-371.

OECD (2010) OECD Health Data September 2010. http://www.oecd-ilibrary.org/statistics. Accessed April 2011

Quick JD, Laing R, and Ross-Degnan D (1991) Intervention research to promote clinically effective and economically efficient use of pharmaceuticals: the international network for rational use of drugs. *Journal of Clinical Epidemiology* 44, II: 57S-65S

Rudholm N (2002) Economic implications of antibiotic resistance in a global economy. *Journal of Health Economics* 21:1071–1083

Sabuncu E, David J, Bernède-Baudin C, Pèpin S, Leroy M, Boëlle PY, Watier L, Guillemot D (2009) Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. *PLoS Medicine* 6, 6:1-9

Tan LJ, Nielsen NH, Young DC, and Trizna Z (2002) Use of antimicrobial agents in consumer products. *Archives of Dermatology* 138: 1082-1086

WHO (2011) ATC/DDD Index 2011. http://www.whocc.no/atc_ddd_index/. Accessed April 2011